

SEP 28 2000

NDA 20-687

Population Council  
Attention: Sandra P. Arnold  
Vice President, Corporate Affairs  
1230 York Avenue  
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, April 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative

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purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

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2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call

Sincerely,

/s/

Center for Drug Evaluation and Research

APPEARS THIS WAY  
ON ORIGINAL

If Mifeprex\* results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions on whom to call and what to do in the event of an emergency following administration of Mifeprex.

Prescribers should make sure that patients receive and have an opportunity to discuss the Medication Guide and the PATIENT AGREEMENT.

**DESCRIPTION**

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11β-[p-(Dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is C<sub>29</sub>H<sub>35</sub>NO<sub>2</sub>. Its structural formula is:

The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 191-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

\* Mifeprex is a trademark of Danco Laboratories, LLC.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamic Activity**

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotrophic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

**Pharmacokinetics and Metabolism**

***Absorption***

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/l occurring approximately 90 minutes after ingestion. The absolute bioavailability of a 20 mg oral dose is 69%.

Mifepristone is 98% bound to plasma proteins, albumin and  $\alpha_1$ -acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

### **Metabolism**

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11 $\beta$ ; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

### **Excretion**

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11 days.

### **Special Populations**

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

### **Clinical Studies**

Safety and efficacy data from the U.S. clinical trials and from two French trials of mifepristone are reported below. The U.S. trials provide safety data on 859 women and efficacy data on 827 women with gestation durations of 49 days or less (dated from the first day of the last menstrual period). In the two French clinical trials, safety evaluable data are available for 1800 women, while efficacy information is available for 1681 of these women. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure, for the U.S. and French studies appear in Table 1.

In the U.S. trials, 92.1% of the 827 subjects had a complete medical abortion, as shown in Table 1. In 52 women (6.3%) expulsion occurred within two days, and resulted from the action of mifepristone (600 mg) alone, unaided by misoprostol, an analog of prostaglandin E<sub>2</sub>. All other women without an apparent expulsion took a 400  $\mu$ g dose of misoprostol two days after taking mifepristone. Many women (44.1%) in the U.S. trials expelled the products of conception within four hours after taking misoprostol and 62.8% experienced expulsion within 24 hours after the misoprostol administration. There were 65 women (7.9%) who received surgical interventions: 13 (1.6%) were medically indicated interventions during the study period, mostly for excessive bleeding; five (0.6%) interventions occurred at the patient's request; 39 women (4.7%) had incomplete abortions at the end of the study protocol; and eight (1.0%) had ongoing pregnancies at the end of the study protocol.

Women who participated in the U.S. trials reflect the racial and ethnic composition of American women. The majority of women (71.4%) were Caucasian, while 11.3% were African American, 10.9% were East Asian, and 4.7% were Hispanic. A small percentage (1.7%) belonged to other racial or ethnic groups. Women aged 18 to 45 were enrolled in the trials. Nearly two-thirds (66.0%) of the women were under 30 years old with a mean age of 27 years.

In the French trials, complete medical abortion occurred in 95.5% of the 1681 subjects, as shown in Table 1. In 89 women (5.3%), complete abortion occurred within two days of taking mifepristone (600 mg). About half of the women (50.3%) in the French trials expelled the products of conception during the first four hours immediately following administration of misoprostol and 72.3% experienced expulsion within 24 hours after taking misoprostol. In total, 4.9% of women in the French trials ultimately received surgical intervention for excessive bleeding, incomplete abortions, or ongoing pregnancies at the end of the protocol.

**Outcome Following**

**Treatment with Mifepristone and Misoprostol in the U.S. and French Trials**

	U.S. Trials		French Trials	
	N	%	N	%
<b>Complete medical abortion</b>	<b>762</b>	<b>92.1</b>	<b>1605</b>	<b>95.5</b>
<u>Timing of expulsion</u>				
Before second visit	52	(6.3)	89	(5.3)
During second visit				
• less than 4 hrs after misoprostol	365	(44.1)	846	(50.3)
After second visit				
• greater than 4 hrs but less than 24 hrs after misoprostol	155	(18.7)	370	(22.0)
• greater than 24 hrs after misoprostol	68	(8.2)	145	(8.6)
Time of expulsion unknown	122	(14.8)	155	(9.2)
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<b>Surgical intervention</b>	<b>65</b>	<b>7.9</b>	<b>76</b>	<b>4.5</b>

Medically necessary interventions during the study period	13	(1.6)	NA	(NA)
Patient request	5	(0.6)	NA	(NA)
Treatment of bleeding during study	NA	(NA)	6	(0.3)
Incomplete expulsion at study end	39	(4.7)	48	(2.9)
Ongoing pregnancy at study end	8	(1.0)	22	(1.3)
<b>Total</b>	<b>827</b>	<b>100</b>	<b>1681</b>	<b>100</b>

*Note: Mifepristone 600 mg oral was administered on Day 1, misoprostol 400 µg oral was given on Day 3 (second visit).*

## INDICATION AND USAGE

Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 µg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS).

## CONTRAINDICATIONS

Administration of Mifeprex and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any one of the following conditions:

- IUD in place (see INDICATION AND USAGE);
- Chronic adrenal failure;
- Concurrent long-term corticosteroid therapy;
- History of allergy to mifepristone, misoprostol or other prostaglandin;
- Hemorrhagic disorders or concurrent anticoagulant therapy;
- Inherited porphyrias.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.

Mifeprex also should not be used by any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen. Patients should be instructed to review the Medication Guide and the PATIENT AGREEMENT provided with Mifeprex carefully and should be given a copy of the product label for their review. Patients should discuss their understanding of these materials with their health care providers, and retain the Medication Guide for later reference (see PRECAUTIONS).

**WARNINGS**

(see CONTRAINDICATIONS)

**1. Bleeding**

Vaginal bleeding occurs in almost all patients during the treatment procedure. According to data from the U.S. and French trials, women should expect to experience bleeding or spotting for an average of nine to 16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more. Bleeding was reported to last for 69 days in one patient in the French trials. In general the duration of bleeding and spotting increased as the duration of the pregnancy increased.

In some cases, excessive bleeding may require treatment by vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions. In the U.S. trials, 4.8% of subjects received administration of uterotonic medications and nine women (1.0%) received intravenous fluids. Vasoconstrictor drugs were used in 4.3% of all subjects in the French trials, and in 5.5% of women there was a decrease in hemoglobin of more than 2 g/dL. Blood transfusions were administered in one of 859 subjects in the U.S. trials and in two of 1800 subjects in the French trials. Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

**2. Confirmation of Pregnancy Termination**

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

**General**

Mifeprex is available only in single dose packaging. Administration must be under the supervision of a qualified physician (see DOSAGE AND ADMINISTRATION).

The use of Mifeprex is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal disease; insulin-dependent diabetes mellitus; severe anemia or heavy smoking. Women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

Although there is no clinical evidence, the effectiveness of Mifeprex may be lower if misoprostol is administered more than two days after mifepristone administration.

**Information for Patients**

Patients should be fully advised of the treatment procedure and its effects. Patients should be given a copy of the Medication Guide and the PATIENT AGREEMENT. (Additional copies of the Medication Guide and the PATIENT AGREEMENT are available by contacting Danco Laboratories at 1-877-4 Early Option) (1-877-432-7596). Patients should be advised to review both the Medication Guide and the PATIENT AGREEMENT, and should be given the opportunity to discuss them and obtain answers to any questions they may have. Each patient must understand:

- the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex;
- that vaginal bleeding and uterine cramping probably will occur;
- that prolonged or heavy vaginal bleeding is not proof of a complete expulsion;
- that if the treatment fails, there is a risk of fetal malformation;
- that medical abortion treatment failures are managed by surgical termination; and
- the steps to take in an emergency situation, including precise instructions and a telephone number that she can call if she has any problems or concerns.

Another pregnancy can occur following termination of pregnancy and before resumption of normal menses. Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

Patient information is included with each package of Mifeprex (see Medication Guide).

**Laboratory Tests**

Clinical examination is necessary to confirm the complete termination of pregnancy after the treatment procedure. Changes in quantitative human Chorionic Gonadotropin (hCG) levels will not be decisive until at least 10 days after the administration of Mifeprex. A continuing pregnancy can be confirmed by ultrasonographic scan.

The existence of debris in the uterus following the treatment procedure will not necessarily require surgery for its removal.

Decreases in hemoglobin concentration, hematocrit and red blood cell count occur in some women who bleed heavily. Hemoglobin decreases of more than 2 g/dL occurred in 5.5% of subjects during the French clinical trials of mifepristone and misoprostol.

Clinically significant changes in serum enzyme (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma-glutamyltransferase (GT)) activities were rarely reported.

## Drug Interactions

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of animals, precluding studies designed to assess effects on fertility during drug administration. Three studies have been performed in rats to determine whether there were residual effects on reproductive function after termination of the drug exposure.

In rats, administration of the lowest oral dose of 0.3 mg/kg/day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effect on reproductive performance was observed. In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth had no adverse effect on future reproductive function in males or females. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. In a separate study in rats, oviduct and ovary malformations in female rats, delayed male puberty, deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency were noted after exposure to mifepristone (1 mg every other day) as neonates.

## Pregnancy

Mifepristone is indicated for use in the termination of pregnancy (through 49 days' pregnancy) and has no other approved indication for use during pregnancy.

## Teratogenic Effects

### Human Data

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Over 620,000 women in Europe have taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 have received mifepristone together with misoprostol. As of May 2000 a total of 82 cases have been reported of which 2 women with on-going pregnancies after using mifepristone alone or mifepristone followed by misoprostol declined to have a surgical procedure at that time. These cases are summarized in Table 2.

**Table 2**  
**Reported Cases (as of May 2000) of On-going Pregnancies Not Terminated by Surgical**

	Abortion at the End of Treatment with Mifepristone Alone or with Mifepristone-Misoprostol		
	Mifepristone Alone	Mifepristone Misoprostol	Total
<b>Subsequently had surgical abortion</b>	3	7	10
<i>No abnormalities detected</i>	2	7	9
<i>Abnormalities detected</i> <i>(sirenomelia, cleft palate)</i>	1	0	1
<b>Subsequently resulted in live birth</b>	13	13	26
<i>No abnormalities detected at birth</i>	13	13	26
<i>Abnormalities detected at birth</i>	0	0	0
<b>Other/Unknown</b>	26	20	46
<b>Total</b>	42	40	82

Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

**Animal Data**

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure level based on body surface area) were carried out. Because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from decreased progesterone levels.

*Nonteratogenic Effects*

The indication for use of Mifeprex in conjunction with misoprostol is for the termination of pregnancy through 49 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

**Nursing Mothers**

It is not known whether mifepristone is excreted in human milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their health care provider to decide if they should

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day three of the treatment procedure. Those adverse events that occurred with a frequency greater than 1% in the U.S. and French trials are shown in Table 3.

Bleeding and cramping are expected consequences of the action of Mifeprex as used in the treatment procedure. Following administration of mifepristone and misoprostol in the French clinical studies, 80 to 90% of women reported bleeding more heavily than they do during a heavy menstrual period (see WARNINGS, Bleeding for additional information). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Pelvic pain, fainting, headache, dizziness, and asthenia occurred rarely. Some adverse reactions reported during the four hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2 to 35% in the U.S. and French trials. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively in the French trials, so that by day 14, reports were rare except for reports of bleeding and spotting.

Table 3

Type of Reported Adverse Events Following Administration of  
Mifepristone and Misoprostol in the U.S. and French Trials\* (percentages)

	U.S. Trials	French Trials
Abdominal Pain (cramping)	96	NA
Uterine cramping	NA	83
Nausea	61	43
Headache	31	2
Vomiting	26	18
Diarrhea	20	12

Dizziness	12	NA
Fatigue	10	NA
Back pain	9	NA
Uterine hemorrhage	5	NA
Fever	4	NA
Viral infections	4	NA
Vaginitis	3	NA
Rigors (chills/shaking)	3	NA
Dyspepsia	3	NA
Insomnia	3	NA
Asthenia	2	1
Leg pain	2	NA
Anxiety	2	NA
Anemia	2	NA
Leukorrhea	2	NA
Sinusitis	2	NA
Syncope	1	NA
Decrease in hemoglobin greater than 2 g/dL	NA	6
Pelvic pain	NA	2
Fainting	NA	2

\* Only adverse reactions with incidence >1% are included

DEAR013

FDA 0015

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1000 mg/kg (about 100 times the human dose recommended for termination of pregnancy).

## **DOSAGE AND ADMINISTRATION**

Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

### **Day One: Mifeprex Administration**

Patients must read the Medication Guide and read and sign the PATIENT AGREEMENT before Mifeprex is administered.

Three 200 mg tablets (600 mg) of Mifeprex are taken in a single oral dose.

### **Day Three: Misoprostol Administration**

The patient returns to the healthcare provider two days after ingesting Mifeprex. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200 µg tablets (400 µg) of misoprostol orally.

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms (see ADVERSE REACTIONS). The patient should be given instructions on what to do if significant discomfort, excessive bleeding or other adverse reactions occur and should be given a phone number to call if she has questions following the administration of the misoprostol. In addition, the name and phone number of the physician who will be handling emergencies should be provided to the patient.

### **Day 14: Post-Treatment Examination**

Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

According to data from the U.S. and French studies, women should expect to experience bleeding or spotting for an average of nine to 16 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at this visit, however, could indicate an incomplete abortion.

Patients who have an ongoing pregnancy at this visit have a risk of fetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures (see PRECAUTIONS, Pregnancy).

Adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol must be reported to Danco Laboratories. Please provide a brief clinical and administrative synopsis of any such adverse events in writing to:

DEAR014

FDA 0016

For immediate consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

## HOW SUPPLIED

Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. Distribution of Mifeprex will be subject to specific requirements imposed by the distributor, including procedures for storage, dosage tracking, damaged product returns and other matters. Mifeprex is a prescription drug, although it will not be available to the public through licensed pharmacies.

Mifeprex is supplied as light yellow, cylindrical, bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. Tablets are packaged in single dose blister packets containing three tablets and are supplied in individual cartons (National Drug Code 6487500103).

Store at 25<sup>0</sup>C (77<sup>0</sup>F); excursions permitted to 15-30<sup>0</sup>C (59-86<sup>0</sup>F) [see USP Controlled Room Temperature].

## Manufactured for:

Danco Laboratories, LLC

P.O. Box 4816

New York, NY 10185

1-877-4 Early Option (1-877-432-7596)

[www.earlyoptionpill.com](http://www.earlyoptionpill.com)

# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*  
**202107Orig1s000**

## **RISK ASSESSMENT and RISK MITIGATION REVIEW(S)**

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**RISK MANAGEMENT REVIEW**

Date: January 27, 2012

Risk Management Analyst: Suzanne Robottom, Pharm.D.  
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D., DRISK

Division Director: Claudia Karwoski, Pharm.D., DRISK

Drug Name: Korlym (mifepristone)

Dosage and Route: 300 mg tablets; by mouth

Application Type/Number: NDA 202-107

Applicant/sponsor: Corcept

OSE RCM #: 2011-2351

## EXECUTIVE SUMMARY

The purpose of this review is to document DRISK's determination that a risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU) is not necessary for the approval of mifepristone for the treatment of the signs and symptoms of endogenous Cushing's syndrome.

Corcept submitted a 505(b)(2) application for approval of Korlym (mifepristone) for the treatment of the signs and symptoms of endogenous Cushing's syndrome. Mifepristone (Mifeprex) is currently approved for pregnancy termination with a REMS with ETASU. Based on FDA feedback provided at the September 14, 2010 pre-NDA meeting, Corcept proposed a REMS with ETASU with their NDA submission.

After extensive research and multiple discussions with the review team, DRISK and the Division of Metabolism and Endocrinology Products (DMEP) determined that:

- A REMS with ETASU is not necessary to ensure that the benefits outweigh the risks of Korlym *in the Cushing's population*.
- A REMS with ETASU for Korlym would not improve the benefit/risk balance for the intended use (Cushing's) population and would add burden.
- Use of Korlym outside of Cushing's syndrome cannot be prospectively quantified.

The REMS Oversight Committee and the Center Director provided additional guidance and affirmed that although a REMS is required for Mifeprex, a REMS for Korlym is not necessary to ensure that the benefits of the drug outweigh its risks at this time. Korlym's safety and drug utilization should use be monitored through post marketing requirements (PMR). If data indicate that the current approach compromises the integrity of the Mifeprex REMS and results in serious adverse events, or additional serious safety signals arise, further regulatory action must be considered.

## 1 INTRODUCTION

The purpose of this review is to document DRISK's determination that a REMS with ETASU is not necessary for the approval of mifepristone for the treatment of the signs and symptoms of endogenous Cushing's syndrome.

### 1.1 BACKGROUND

Corcept submitted a 505(b)(2) application on April 15, 2011 for approval of Korlym (mifepristone) to treat the clinical and metabolic effects of hypercortisolism in adult patients ( $\geq 18$  years of age) with endogenous Cushing's syndrome including:

- Patients with Cushing's disease who have not adequately responded to or relapsed after surgery
- Patients with Cushing's disease who are not candidates for surgery

(b) (4)

Korlym is manufactured as 300 mg tablets. The proposed dosing for the aforementioned indication is 300 to 1200 mg daily by mouth.

## 1.2 REGULATORY HISTORY

Mifepristone is currently marketed as Mifeprex and approved on September 28, 2000 under 21 CFR 314 Subpart H for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The approved dosing is 600<sup>1</sup> mg (three (3), 200 mg tablets) followed by misoprostol on Day 4. Since approval, mifepristone is available only through a restricted distribution program that requires prescribers to be enrolled to be able to order Mifeprex and should only be distributed to/through a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. Mifeprex is not distributed to or dispensed through retail pharmacies. The restricted distribution program was approved as a REMS on June 8, 2011.<sup>2</sup>

In 2007, Corcept initiated a clinical development program to evaluate the clinical benefit of mifepristone in patients with Cushing's syndrome and received orphan drug designation on July 5, 2007.

A pre-NDA meeting with Corcept was held on September 14, 2010. Corcept informed the FDA that they intended to submit a REMS and requested comments on the draft REMS. The FDA informed Corcept that for this NDA/indication, a REMS with restricted distribution would be necessary to address the risk of termination of pregnancy. The proposed REMS must be sufficient to maintain the integrity of the current Mifeprex restricted distribution program. The sponsor was instructed that a complete review of the proposed REMS, and REMS materials would be done in conjunction with the full clinical review after the NDA is submitted.

On April 15, 2011 Corcept submitted NDA 202107 for review with a proposed REMS.

## 2 MATERIALS REVIEWED

The following materials were reviewed:

- Weber J. Pre-NDA Meeting Preliminary Comments for September 14, 2010. Signed under IND 76480 on September 9, 2010 by Weber J.
- NDA 202107 submitted on April 15, 2011 and received on April 18, 2011 with a proposed REMS with ETASU.
- Bhatnagar U. Maternal Health Team review for Mifepristone. Signed September 15, 2011 by Bhatnagar U, Feibus K, and Mathis L.
- Greene P. Drug use review of Mifeprex. Signed September 19, 2011 by Greene P, Chai G, and Governale L.

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<sup>1</sup> Standard practice is to dispense a single, 200 mg tablet of mifepristone, not 600 mg. In addition, the standard misoprostol dose is 800µg (4 tablets), not 400 µg.

<sup>2</sup> Mifepristone was included on the list of products deemed to have in effect an approved risk evaluation and mitigation strategy (REMS) under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

- November 3, 2011 Center Director Briefing on Mifepristone for Cushing's syndrome. Signed into DAARTS for NDA 202107 on November 15, 2011 by Egan A.
- (b) (6) Division of Reproductive and Urology Products consult response. Signed November 18, 2011 by (b) (6).

### 3 RISK BENEFIT CHARACTERIZATION

#### 3.1 CUSHING'S SYNDROME AND TREATMENT OPTIONS

Cushing's syndrome is a serious, multisystem disorder that results from overproduction of cortisol by the adrenal glands. For those not cured by surgery, it is a chronic and debilitating condition.<sup>4</sup> If left untreated, Cushing's syndrome limits survival to 4 to 5 years following initial diagnosis.<sup>3</sup>

Surgical resection of the offending tumor remains first line treatment, and initial cure or remission is obtained in 65-85% of patients with Cushing's disease.<sup>4</sup> In cases that surgery only partially or temporarily controls glucocorticoid hypersecretion (or for patients who are not candidates for surgery),<sup>5</sup> radiation and/or pharmacologic treatment is used for disease control. A two to three fold increase in mortality is observed in most studies and this excess mortality seems confined to patients in whom initial cure was *not* obtained (the indicated population for mifepristone).<sup>4</sup>

There is an unmet medical need for additional drug treatment options for Cushing's syndrome. The following table lists the drug treatment options, none of which are approved for Cushing's syndrome:<sup>2,6</sup>

Steroidogenic inhibition	Adrenolytic	Neuromodulators of ACTH release	Glucocorticoid receptor antagonism
<ul style="list-style-type: none"> <li>• Metyrapone (not available in US)</li> <li>• Aminogluthethimide (discontinued)<sup>^</sup></li> <li>• Ketoconazole</li> </ul>	<ul style="list-style-type: none"> <li>• Mitotane<sup>^^</sup></li> <li>• Etomidate</li> </ul>	<ul style="list-style-type: none"> <li>• Cyproheptidine*</li> <li>• Bromocriptine*</li> <li>• Valproic acid*</li> <li>• Octreotide*</li> </ul>	<ul style="list-style-type: none"> <li>• Mifepristone</li> </ul>
<sup>^</sup> Aminogluthethimide was approved in 1980 and indicated "for the the suppression of adrenal function in selected patients with Cushing's syndrome." <sup>^^</sup> Mitotane was approved in 1970 and indicated for "the treatment of inoperable adrenal cortical carcinoma of both functional and nonfunctional types." *Agent has <u>not</u> demonstrated consistent clinical efficacy. <sup>3</sup>			

<sup>3</sup> Gums JG, Smith JD. Adrenal Gland Disorders. Pharmacotherapy: A pathophysiologic approach. 4<sup>th</sup> ed. Ed Dipro JT. Stamford, Appleton & Lange, 1999. Print.

<sup>4</sup> Steffensen C, Bak AM, Rubeck KZ, Jorgensen JO. Epidemiology of Cushing's syndrome. Neuroendocrinology 2010;92(supp 1):1-5.

<sup>5</sup> Johanssen S, Allolio B. Mifepristone (RU 486) in Cushing's syndrome. Euro J Endocrin (2007)156; 561-569.

<sup>6</sup> Heyn J, et al. Medical suppression of hypercortisolemia in Cushing's syndrome with particular consideration for etomidate. Pituitary (online May 10, 2011).

### **3.1.1 Size of Population**

Cushing's syndrome is a rare disorder with incidence ranging from 0.7 to 2.4 per 1 million persons per year.<sup>7</sup> Ninety percent of all cases of Cushing's syndrome occur during adulthood; the incidence of Cushing's syndrome in children is estimated at approximately 0.2 cases per 1 million persons per year.

It is estimated that at any given time there are approximately 20,000 patients with Cushing's syndrome in the U.S. The peak incidence of Cushing's syndrome due to an adrenal or pituitary tumor occurs in persons 25-40 years of age; females are 8 times more likely than males to develop hypercortisolemia from a pituitary tumor and 3 times more likely to develop a cortisol-secreting adrenal tumor.

In the US, it is estimated that approximately 5,000 patients would be considered candidates for treatment with Korlym.

### **3.2 EXPECTED DRUG BENEFIT**

Mifepristone works by binding to glucocorticoid receptors, preventing cortisol from binding, and thereby blocking cortisol's activity and effects. It does not decrease the amount of circulating cortisol. It has a rapid onset of action (~90 minutes for peak plasma concentrations).

According to the sponsor in Study 400 (open label, 24 week prospective trial), 60% of the diabetes patients met the primary endpoint of at least a 25% reduction in AUC<sub>glucose</sub>, and antidiabetic medication use was reduced in half of the patients. The Data Review Board determined that 72% of patients met the secondary endpoint of a change in signs and symptoms at week 24.

Mifepristone may be used as an adjunct to radiation, palliative treatment, or when rapid onset of anti-glucocorticoid effect is required (e.g., psychosis).

### **3.3 DURATION OF TREATMENT**

Cushing's syndrome that is not cured by surgery is a chronic condition. Patients may be treated indefinitely (weeks, months, years/decades) with mifepristone.

### **3.4 SEVERITY OF THE RISK**

The observed risks (adverse events documented in the safety database; adrenal insufficiency, hyopkalemia, and endometrial hyperplasia) in patients with Cushing's syndrome were considered. After discussion with DMEP, we agree that these risks can be adequately addressed through labeling.

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<sup>7</sup> Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. Lancet. 2006 May 13;367(9522):1605-17.

Two risks were identified that are anticipated to occur in the post-marketing setting. These risks were the focus of the risk management discussion.

### 3.4.1 Fetal Loss (unintended pregnancy termination)

#### 3.4.1.1 *Cushing's Syndrome Patients*

Mifepristone blocks progesterone receptors at lower doses than necessary for glucocorticoid receptor inhibition. Therefore, the lowest treatment dose studied for the treatment of Cushing's syndrome is effective for terminating pregnancy. However, mifepristone alone is less effective for pregnancy termination when compared to the combined regimen mifepristone/prostaglandin.<sup>8</sup>

Women with Cushing's syndrome are not at substantial risk for fetal loss because they are unlikely to be pregnant. The review by the Maternal Health Team (MHT) states that amenorrhea and ovulatory disturbances are associated with untreated Cushing's syndrome and therefore pregnancy occurs "rarely" in this population. Pregnancy may occur in a small subset of patients with Cushing's syndrome who are of childbearing age. MHT recommends that this possibility be noted in labeling.<sup>9</sup>

At the time treatment is initiated with mifepristone, a woman has a low likelihood of conception due to her underlying disease. During treatment, if she is not compliant with mifepristone treatment, she would be amenorrheic due to worsened disease condition. If she is compliant with medication, mifepristone would prevent a sustained pregnancy. Therefore, the risk of fetal loss before and during treatment in the intended patient population appears low.

Pregnancy tests were performed in Study 400 as part of enrollment and repeated after any significant interruption of treatment. No pregnancies were reported.

#### 3.4.1.2 *Non-Cushing's Syndrome Patients*

There are a variety of uses for mifepristone (b) (4). It has been studied to treat the following:

(b) (4)

(b) (4)

<sup>8</sup> (b) (6) Division of Reproductive and Urology Products consult response. Signed November 18, 2011 by (b) (6)

<sup>9</sup> Bhatnagar U. Maternal Health Team review for Mifepristone. Signed September 15, 2011 by Bhatnagar U, Feibus K, and Mathis L.

At present, mifepristone is only commercially available in blister packages (3 pills per carton) that are sold through the Mifeprex REMS. If Korlym is approved without restrictions (e.g. REMS), mifepristone will be more readily available to treat females of child bearing potential with other chronic conditions. The extent of off-label use of mifepristone, for the above conditions, in the post-marketing setting is unknown.

### **3.4.2 Intended Termination of Pregnancy with Korlym**

If Korlym is approved without a REMS with restricted distribution, there will be increased access to mifepristone. This could lead to 1) prescribers prescribing Korlym for the termination of pregnancy without following the safeguards that are in place for Mifeprex and/or 2) misuse, pilfering, and diversion of Korlym for the termination of pregnancy not under the supervision of a healthcare provider.

The risk mitigation tools for the Mifeprex REMS are physician certification and controlled access to assure safe use. A Mifeprex prescriber must agree that he/she meets the required qualifications to assure the drug is used safely and appropriately. Compliance with the REMS requirements is not enforced beyond a one-time completion of the enrollment form (e.g., signed Patient Agreements are not collected). The certification requirement is the tool that provides controlled access for Mifeprex. Without restricted distribution, a prescriber using Korlym for pregnancy termination would not have to attest to having certain skills, agree to document certain information/activities, or report adverse events. The patient would not receive a Patient Agreement or Mifeprex Medication Guide that would provide the most relevant and important information to her for pregnancy termination. The current REMS does not prevent use beyond 49 days gestation, termination of an ectopic pregnancy, bleeding, incomplete abortion, and infection.

In considering if there is increased potential for pilfering and misuse with Korlym, we note that Mifeprex is distributed only to medical facilities and dispensed to the patient in small quantities (a single tablet) by certified prescribers. Korlym will be distributed directly to patients, in larger quantities and each Korlym tablet is an effective dose for pregnancy termination. Moreover, Korlym is proposed to be packaged in bottles of 28 and 280, making diversion and pilfering presumably easier relative to the Mifeprex packaging. Similar to Korlym, there is potential for Mifeprex to be pilfered or diverted from a distribution facility, during shipping, or at the place of dispensing. Mifeprex has processes in place to prevent drug loss during distribution and shipping that can be done outside a REMS for Korlym. It is not known if clinics keep careful stock and dispensing records of Mifeprex.

### **3.5 RISK IN CONTEXT OF DRUGS IN CLASS AND AMONG OTHER DRUGS USED TO TREAT THE DISEASE**

There are no other glucocorticoid receptor antagonists approved in the U.S. for comparison.

Ketoconazole, metapyrone (not approved in U.S.), mitotane, etomidate are anti-corticoid drugs that are used for the treatment of Cushing's syndrome. Because these drugs have a

different mechanism of action, they are not associated with the same potential risks as mifepristone. These drugs are associated with serious risk(s) although none of these drugs have a REMS.

### **3.6 HOW THE RISK(S) ARE MANAGED ACROSS OTHER PRODUCTS AND/OR DISEASES**

#### **3.6.1 Fetal Loss**

Other drug products are associated with fetal loss (e.g., methotrexate, misoprostol; see Attachment 1). At present, this risk is addressed through labeling for these drugs. There are no REMS approved that address only fetal loss without also the accompanying risk of birth defect.

#### **3.6.2 Intended Termination of Pregnancy with Korlym**

We identified two drugs, misoprostol and methotrexate, that are associated with a risk of pregnancy termination and are approved for other uses. See the table in Attachment 1. The extent to which misoprostol and methotrexate are used off-label to terminate pregnancy is unknown. With each drug, the risk of termination of pregnancy is managed through labeling (Contraindication, Boxed Warning) and neither product has a REMS.

#### **3.6.3 Misuse**

Misuse has been addressed in different ways as follows:

##### *Voluntary Restricted Distribution:*

- *Example: Egrifta/growth hormone:* Growth hormones are at risk for misuse and abuse. None of the growth hormone products have a REMS. However, the sponsor has voluntarily decided to distribute this product through a non-REMS restricted distribution system which allows tracking “of each box of Egrifta to determine the volume of product dispensed and evaluate if the projected number of boxes dispensed correlates with prescription use in the intended population.”<sup>10</sup> Egrifta was approved in 2010 with no REMS and no PMR for monitoring drug use.

##### *Required Restricted Distribution Program*

- *Example: Xyrem*<sup>11</sup>
  - At the time Xyrem was initially approved in 2002, the Sponsor agreed as a condition of approval to distribute and dispense Xyrem through a primary and exclusive central pharmacy, implement a program to educate physicians and patients about the risks and benefits of Xyrem, fill the initial prescription only after the prescriber and patient received and read the educational materials, and maintain patient and prescribing physician registries.<sup>12</sup>

<sup>10</sup> LaCivita C. Review of REMS for Egrifta. Signed September 3, 2010.

<sup>11</sup> Xyrem was included on the list of products deemed to have in effect an approved risk evaluation and mitigation strategy (REMS) under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007.

<sup>12</sup> Choudhry Y. REMS Interim Comment Set #1. Signed August 1, 2011 by Choudhry Y and Worthy K.

### **3.6.4 Same Active Ingredient, Different Indication and Different Risk Management Approaches**

The agency evaluates an active ingredient based on the risk benefit profile for the intended population. To date, the Agency has not required a REMS for a product based only on the fact that the active ingredient already has a REMS for one population. For example, denosumab was originally approved under two tradenames for different indications. Prolia was initially approved for the treatment for post-menopausal osteoporosis (PMO). At that time, a REMS for Prolia was required and approved consisting of a Medication Guide and communication plan to “inform healthcare providers about the risks of serious infections, dermatologic adverse reactions, and suppression of bone turnover, including osteonecrosis of the jaw.” Under the tradename Xgeva, denosumab was approved for prevention of skeletal-related events in patients with bone metastases from solid tumors. A REMS was not required given the resulting differences in the risk benefit profile when considering the patient populations (post-menopausal women vs cancer patients with bone metastases) and prescribing populations (internists vs oncologists).

### **3.7 PRODUCTS AFFECTED**

Mifeprex (and pending generics) are potentially affected because they are or will only be available under a restrictive REMS.

## **4 RISK MANAGEMENT CONSIDERATIONS**

The following factors are important to consider:

- Burden to the intended population

It is important to ensure that the intended treatment population can receive Korlym in a timely, dependable manner in the least burdensome way. Any restrictions will impede access with little to no benefit to Cushing’s syndrome population.

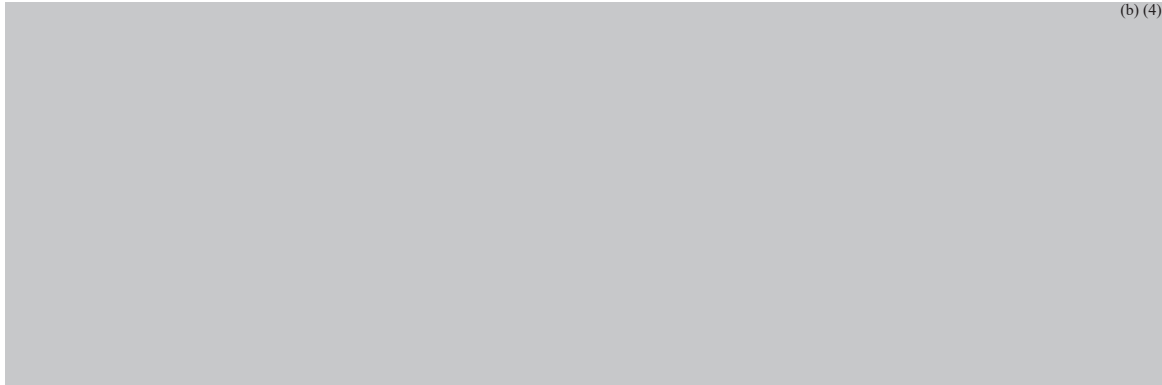
- Confidentiality/Privacy

Confidentiality and patient privacy is a significant issue with Mifeprex. To what extent do stakeholders who make, distribute, dispense, prescribe, and use Korlym need protection from a confidentiality perspective?

The purpose of a REMS is to ensure the benefits of the drug outweigh its risks. Confidentiality and concern regarding the safety of the prescribers, pharmacists, and patients does not meet criteria. Confidentiality can be maintained without a REMS. Privacy may be better maintained if there are no systems in place to track formally prescribers and patients. Risk to pharmacies that stock the drug should be considered but it is outside the purview of a REMS.

- Reproductive potential for various possible Korlym off-label use populations

As stated in section 3.4.1.2. above, there are a variety of uses for mifepristone (b) (4). The therapeutic areas included below are more likely to include females of reproductive potential than other uses (b) (4). A formal epidemiologic review was not conducted to estimate of the proportion of females of reproductive potential for each use. However, the following observations and/or assumptions were made:



The degree to which Korlym will be used off label for the above uses is unknown.

- Extent of current off-label use

Current Mifeprex drug utilization information is not informative in predicting broader uses for Korlym. In the September 19, 2011 mifepristone drug use review using commercial databases was conducted, off-label use was described as “uncommon” based on information obtained through a *sample* of medical offices and outpatient clinics. Sales distribution data was not available. The lack of findings are not surprising given the design of the Mifeprex REMS.

## 5 RISK MANAGEMENT OPTIONS

DRISK analyzed more than six risk management options to address intended termination of pregnancy by:

- HCPs outside of Mifeprex REMS
- women who seek to terminate a pregnancy and are not under the care of an HCP

Ultimately, three options were considered.

1. No REMS and voluntary restricted distribution through specialty pharmacies/distributors

This REMS option may minimize diversion and subsequent misuse by minimizing the number of pharmacies stocking and dispensing Korlym for outpatient use. This option is in alignment with DMEP and DRISK’s assessment that a REMS is not necessary to assure the safe use of mifepristone for treating patients with Cushing’s syndrome because we believe the likelihood that a Cushing’s patient experiences “serious complications” relating to pregnancy termination are low.

This approach is also consistent with misoprostol and methotrexate, both of which are known abortifacents and do not have a REMS to address that risk. This approach is used to prevent misuse of the growth hormone products.

**2. REMS with ETASU – dispensing through certified specialty pharmacies**

This REMS option may minimize diversion and subsequent misuse by minimizing the number of pharmacies stocking and dispensing Korlym for outpatient use. In addition, Corcept would be required to provide FDA an assessment of how the REMS is achieving its goals.

This option does not address intended termination of pregnancy with Korlym.

**3. REMS with ETASU – prescriber certification (agreement not to use for termination of pregnancy) and distribution through certified specialty pharmacies that are willing to track inventory**

This REMS option would minimize diversion and subsequent misuse as described above. In addition, certified pharmacies (for outpatient dispensing, not inpatient hospital pharmacies) would verify that prescribers were certified. Prescriber certification would consist of agreement not use Korlym for pregnancy termination. The addition of prescriber certification would address the risk of intended termination of pregnancy with Korlym.

These options assume that the safety labeling is maximized to address Korlym use in pregnancy.

## **6 DISCUSSION**

The issue of how to address intended termination of pregnancy was discussed at the REMS Oversight Committee meeting on September 29, 2011 and at a Center Director Briefing on November 3, 2011.

DMEP and DRISK presented at both meetings that women with Cushing's syndrome are unlikely to be or become pregnant given the effects of their disease on the reproductive system and the effects of daily mifepristone treatment. Therefore, addressing the risk of fetal loss associated with Korlym was not discussed because 1) pregnancy is not a likely event in the intended population and; 2) the use of Korlym for "off-label" uses (in women more likely to be pregnant) is unknown and available data do not indicate that mifepristone would be first line treatment for any diseases or conditions at this time. For these reasons, there was general agreement that fetal loss can be adequately addressed through labeling and is not necessary to require additional safe use measures through a REMS at this time.

The team stated that for any risk management approach, it is important to ensure that the intended treatment population can receive Korlym in a timely, dependable manner in the least burdensome way. Any restrictions could impede access without benefit to the intended population.

The primary focus shifted to whether or not a REMS is necessary for Korlym to maintain the integrity of the Mifeprex REMS. While the absence of any restrictions on Korlym could undermine the safe use conditions required by the Mifeprex REMS, a number of other factors are important considerations including:

- The burden (reduced access, treatment delays) of a restrictive REMS to the Cushing's population without any benefit from the REMS for this population.
- Overall drug exposure and subsequent access is anticipated to be small given the small size of the intended use population and lack of a signal for substantially broader use.
- The sponsor's plan to distribute Korlym through a specialty pharmacy regardless of the REMS. If necessary, this provides the sponsor the ability to monitor use more closely.
- The cost - If the cost of this orphan product is substantial, it may be expensive to obtain and deter use for pregnancy termination as well as other off label uses. In addition, third party payors/reimbursement may play a substantial role in influencing prescribing behavior. It is unknown how much Korlym will cost and how cost will impact prescribing behavior.<sup>13</sup>

The need for some monitoring of use was discussed. Commercial drug use databases will not provide FDA with adequate estimates of Korlym use because Korlym will be dispensed through a specialty pharmacy. As noted above, using a single specialty pharmacy does allow the sponsor the ability to monitor use more closely through its business contract with the specialty pharmacy. Similarly, commercial drug use databases are not able to provide an accurate estimate of Mifeprex use due to how it is distributed and dispensed. The first REMS assessment for Mifeprex is due June 2012 which we anticipate will provide a baseline to quantify current Mifeprex use. Given these considerations and the discussion with the Center Director, we agree that a post-marketing requirement (PMR) study to obtain Korlym use data (age, gender, dose, duration of treatment) "to better characterize the incidence rates of adverse events with Korlym" is prudent. Monitoring drug use data for both Mifeprex and Korlym, in conjunction with reports of serious adverse events resulting from pregnancy terminations outside of the Mifeprex REMS, will be important factors in future regulatory action to address any compromise to the Mifeprex REMS.

## 7 CONCLUSION

A REMS for Korlym is not necessary to ensure that the benefits of the drug outweigh its risks at this time. We agree that it is prudent to monitor use through a PMR. If data indicate that this approach compromises the integrity of the Mifeprex REMS and results in serious adverse events, or additional serious safety signals arise, further regulatory action must be considered.

## ATTACHMENTS

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<sup>13</sup> Planned parenthood charges \$300-800 for a medical abortion (includes diagnostic testing, mifepristone, and misoprostol).

ATTACHMENT 1: Drugs with a risk associated with an off-label use

Drug	Abortifacient Efficacy	Indication	Off-label use*	Contraindication	Boxed Warning
Misoprostol (Cytotec)	When used alone – variable (~40-60%); used in combination with MTX or MFP efficacy is higher  (Source - Micromedex)	NSAID-induced gastric ulcers	<ul style="list-style-type: none"> <li>• Postpartum hemorrhage</li> <li>• Cervical ripening, labor induction</li> <li>• Pregnancy termination</li> </ul>	“Cytotec should not be taken by pregnant women to reduce the risk of ulcers induced by NSAIDs ”	“Cytotec administration to women who are pregnant can cause abortion ... Cytotec should not be taken by pregnant women to reduce the risk of ulcers induced by NSAIDs... Patients must be advised of the abortifacient property and warned not to give the drug to others ... ”
Methotrexate (MTX)	When used alone – (IM injxn – variable); in combination with misoprostol efficacy is higher (80-90%; small Ns)  (Source - Micromedex)	<ul style="list-style-type: none"> <li>• Cancer</li> <li>• Psoriasis</li> <li>• Rheumatoid arthritis including juvenile</li> </ul>	<ul style="list-style-type: none"> <li>• Other Autoimmune diseases</li> <li>• More cancer</li> <li>• Pregnancy termination</li> </ul>	“MTX can cause fetal death or teratogenic effects when administered to a pregnant woman MTX is contraindicated in pregnant women with psoriasis or rheumatoid arthritis and should be used in the treatment of neoplastic diseases only when the potential benefit outweighs the risk to the fetus Women of childbearing potential should not be started on MTX until pregnancy is excluded and should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment ”	“MTX has been reported to cause fetal death and/or congenital anomalies Therefore, it is not recommended for women of childbearing potential unless there is clear medical evidence that the benefits can be expected to outweigh the considered risks Pregnant women with psoriasis or rheumatoid arthritis should not receive MTX ”

\*The off-label uses are general and based on tertiary sources; not on a formal drug use analysis.

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/s/  
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SUZANNE C BERKMAN ROBOTOM  
01/27/2012

CLAUDIA B KARWOSKI  
01/27/2012  
concur

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### ***APPLICATION NUMBER:***

020687Orig1s020

***Trade Name:*** Mifeprex Tablets

***Generic Name:*** mifepristone

***Sponsor:*** Danco Laboratories, LLC

***Approval Date:*** March 29, 2016

***Indication:*** For use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 020687Orig1s020

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# **CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**020687Orig1s020**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 020687/S-020

**SUPPLEMENT APPROVAL**

Danco Laboratories, LLC

(b) (6)

P.O. Box 4816  
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated July 17, 2015.

This "Prior Approval" supplemental new drug application proposes to provide for use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS.

**APPROVAL & LABELING**

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because the use of this product before menarche is not indicated, and we have determined that you have fulfilled the pediatric study requirement for post-menarcheal patients.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The REMS consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS included revisions to both the prescriber and patient agreement forms.

Other changes proposed in the efficacy supplement prompted additional revisions to the Mifeprex REMS materials. During review of this efficacy supplement, we also assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks.

After consultations between the [REDACTED] (b) (6) and the [REDACTED] (b) (6) [REDACTED] we have determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS. The REMS modifications submitted by you on March 29, 2016 are approved.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Mifeprex outweigh its risks. The

Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on July 17, 2015, and appended to this letter, is approved as amended. The modified REMS consists of elements to assure safe use (A, C and D), an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on June 8, 2011.

The REMS assessment plan will include the information submitted to FDA on March 29, 2016.

The revised REMS assessment plan must include, but is not limited to, the following:

**REMS Assessment Plan**

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative).
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

NDA 020687/S-020  
Page 5

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 020687 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 020687/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 020687/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 020687/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

*or*

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 020687/S-000  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISIONS FOR NDA 020687**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call

(b) (6)

Sincerely,

*{See appended electronic signature}*

(b) (6)

Center for Drug Evaluation and Research

NDA 020687/S-020  
Page 7

ENCLOSURES:

Content of Labeling  
REMS

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/s/  
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(b) (6)

03/29/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 020687/S-014

**SUPPLEMENT APPROVAL**

Danco Laboratories, LLC

(b) (6)

P.O. Box 4816  
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated September 16, 2008, received September 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MIFEPREX<sup>®</sup> (mifepristone) Tablets. We note that NDA 020687 is approved under the provisions of 21 CFR 314.520 (Subpart H).

This supplemental application provides for a proposed risk evaluation and mitigation strategy (REMS) for MIFEPREX (mifepristone) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified MIFEPREX (mifepristone) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We acknowledge receipt of your amendments dated December 9, 2008, November 8, 2010, and May 19 and 27, 2011.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications.

Your proposed REMS, as amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

NDA 020687/S-014  
Page 2

The REMS assessment plan will include the information submitted to FDA on May 27, 2011, and should include the following information:

- a. Per section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
- b. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify future submissions containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 020687  
PROPOSED REMS MODIFICATION  
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 020687  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

As part of the approval under Subpart H, as required by 21 CFR 314.550, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days

NDA 020687/S-014  
Page 3

before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the (b) (6) and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, (b) (6)

Sincerely,

*{See appended electronic signature page}*

(b) (6)

**ENCLOSURES:**

REMS Document  
REMS Materials

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/s/

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(b) (6)

06/08/2011

ARUN G. RAO  
Deputy Assistant Attorney General

GUSTAV W. EYLER  
Director

HILARY K. PERKINS  
Assistant Director

JONATHAN E. AMGOTT (DCBN 1031947)  
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Washington, D.C. 20530  
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*Attorneys for Defendants Xavier Becerra, et al.  
(see signature page for complete list)*

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF HAWAII

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

v.

XAVIER BECERRA, J.D., *in his  
official capacity as* SECRETARY,  
U.S. D.H.H.S., *et al.*,

Defendants.

CIV. NO. 1:17-00493 JAO-RT

**JOINT MOTION TO STAY CASE  
PENDING AGENCY REVIEW**

District Judge: Jill A. Otake  
Summary Judgment Hearing: July 9,  
2021, at 9:00 AM  
Trial Date: Vacated per Dkt. 82

The Parties jointly seek a stay of this matter in light of Defendant U.S. Food and Drug Administration’s (“FDA”) current review of the risk evaluation and mitigation strategy (“REMS”) at issue in this case. The Parties agree that the outcome of FDA’s review could have a material impact on the course of this litigation. Accordingly, to conserve the resources of the Court and the Parties, the Parties seek a stay of this matter until December 1, 2021, with a joint status report, to include an update on the status of FDA’s review, due on November 1, 2021.

FDA is reviewing the elements of the REMS for Mifeprex and its approved generic, Mifepristone Tablets, 200 mg, in accordance with the REMS assessment provisions of Section 505-1 of the Federal Food, Drug, and Cosmetic Act. In conducting this review, FDA is relying on information submitted by the sponsors of the new drug application (“NDA”) and the abbreviated new drug application (“ANDA”) and information from other sources, including published literature. FDA also commits to review any relevant data and evidence submitted by the Plaintiffs.

FDA recently completed a review of the in-person dispensing requirement (and related provisions) of the REMS in the context of the COVID-19 public health emergency (“PHE”). On April 12, 2021, in response to an April 2020 request from the American College of Obstetricians and Gynecologists (“ACOG”), the Agency decided that it intends to exercise enforcement discretion with respect

to the in-person dispensing requirement (and related provisions) during the pendency of the PHE.

In a letter announcing its decision, FDA stated that “provided the other requirements of the Mifepristone REMS Program are met,” the Agency “intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.” Joint Stips. of Facts, Ex. J, at 2, Dkt. 140-10. FDA also stated that, “to the extent all of the other requirements of the Mifepristone REMS Program are met,” the Agency “intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.” *Id.* If FDA’s review of the REMS is not completed before the expiration of the PHE, FDA agrees that it intends to exercise this enforcement discretion for a further 30 days following the end of the PHE to afford an opportunity for the mifepristone drug sponsors and mifepristone prescribers to modify their operational protocols.

In light of FDA’s decision, the parties in *ACOG v. FDA*, No. 8:20-cv-1320-TDC (D. Md.), recently filed a joint status report indicating that the plaintiffs intend to voluntarily dismiss their case challenging the restricted dispensing

requirement (and related provisions) during the PHE. The parties also stated their intention to jointly move for dismissal of appeals pending in the U.S. Court of Appeals for the Fourth Circuit, No. 20-1784.

Similarly, the outcome of FDA’s review of the REMS could have a material effect on the issues before this Court. Thus, to conserve the resources of the Court and the Parties, the Parties jointly seek a stay of proceedings until December 1, 2021. *See, e.g., Leyva v. Certified Grocers of Cal., Ltd.*, 593 F.2d 857, 863 (9th Cir. 1979) (recognizing district court authority to stay litigation in the interest of efficiency and fairness “pending resolution of independent proceedings which bear upon the case”); EO (Jan. 23, 2020), Dkt. 107.

Previously, the Court stayed this case *sua sponte* pending the Supreme Court’s ruling in *June Medical Services, L. L. C. v. Russo*, 140 S. Ct. 2103 (2020). *See* EO (Jan. 23, 2020), Dkt. 107; EO (Jan. 13, 2020), Dkt. 102. Following the *June Medical* decision and certain proceedings in the *ACOG* litigation, the Court recently lifted its stay in response to Plaintiffs’ unopposed motion. *See* EO (Mar. 5, 2021), Dkt. 128; Pls.’ Unopposed Mot. to Lift Stay & Reactivate Summ. J. Briefing, Dkt. 127. Plaintiffs made their request to lift the stay, however, prior to FDA’s April 2021 decision and prior to FDA’s current review of the REMS. In light of these developments, the stay presently sought by the Parties would once again enable the Court to handle this case “with economy of time and effort for

itself, for counsel, and for litigants.” *Landis v. N. Am. Co.*, 299 U.S. 248, 254 (1936).

For the foregoing reasons, the Parties respectfully propose that the Court enter an Order: (1) staying this litigation until December 1, 2021; (2) directing the Parties to submit a joint status report by November 1, 2021; and (3) permitting any Party to move to lift or extend the stay for good cause.



ARUN G. RAO  
Deputy Assistant Attorney General

GUSTAV W. EYLER  
Director

HILARY K. PERKINS  
Assistant Director

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*Attorneys for Defendants Xavier Becerra, J.D.,  
in his official capacity as Secretary,  
U.S. Department of Health and Human Services;  
U.S. Food and Drug Administration; and  
Janet Woodcock, M.D., in her official capacity as  
Acting Commissioner of Food and Drugs*

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF HAWAII

GRAHAM T. CHELIUS, M.D., *et al.*,

Plaintiffs,

v.

XAVIER BECERRA, J.D., *in his  
official capacity as* SECRETARY,  
U.S. D.H.H.S., *et al.*,

Defendants.

CIVIL NO. 17-00493 JAO-RT

**ORDER GRANTING JOINT  
MOTION TO STAY CASE  
PENDING AGENCY REVIEW**

The parties jointly seek a stay of this matter in light of Defendant U.S. Food and Drug Administration’s current review of the risk evaluation and mitigation strategy (“REMS”) at issue in this case. After reviewing the parties’ Joint Motion to Stay Case Pending Agency Review, ECF No. 148, and for good cause shown, the Court GRANTS the parties’ Joint Motion. This litigation is stayed until December 1, 2021. The parties are directed to submit a joint status report every 90 days, starting on August 5, 2021. Any party may move to lift or extend the stay for good cause.

IT IS SO ORDERED.

DATED: Honolulu, Hawai‘i, May 7, 2021.



A handwritten signature in black ink, reading "Jill A. Otake".

Jill A. Otake  
United States District Judge

CV 17-00493 JAO-RT, *Chelius, et al. v. Becerra, et al.*; ORDER GRANTING JOINT MOTION TO STAY CASE PENDING AGENCY REVIEW



NDA 020687

## REMS MODIFICATION NOTIFICATION

Danco Laboratories, LLC  
(b) (4), (b) (6)

P.O. Box 4816  
New York, NY 10185

Dear (b) (4), (b) (6):

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprrex (mifepristone) Tablets.

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

The REMS for mifepristone was originally approved on June 8, 2011, and your single shared system REMS (SSS REMS) was approved on April 11, 2019. Your last SSS REMS modification was approved May 14, 2021. The SSS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID 19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

**Elements to Assure Safe Use:** We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in person dispensing requirement") is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in person dispensing will also minimize the burden on the healthcare delivery system of complying with the REMS.

**Elements to Assure Safe Use:** Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of serious

NDA 020687

Page 2

complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe use conditions.

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS must include a timetable for submission of assessments. The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS, and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your NDA.

NDA 020687

Page 3

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR NDA 020687/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687/S-000  
PROPOSED REMS MODIFICATION-AMENDMENT**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

**SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email [FDAREMSwebsite@fda.hhs.gov](mailto:FDAREMSwebsite@fda.hhs.gov).

NDA 020687

Page 4

If you have any questions, call (b) (6), at (b) (6).

Sincerely,

*{See appended electronic signature page}*

(b) (6)

Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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(b) (6)

12/16/2021 03:09:07 PM

DEAR058

2021 REMS 001807



**FDA U.S. FOOD & DRUG**  
ADMINISTRATION

ANDA 091178

## REMS MODIFICATION NOTIFICATION

GenBioPro, Inc.

c/o

(b)(4)/TS-CI; (b)(6)/PPI

Attention:

(b)(4)/TS-CI; (b)(6)/PPI

Dear (b)(4)/TS-CI; (b)(6)/PPI :

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for mifepristone tablets.

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

The Shared System (SS) REMS for mifepristone consists of elements to assure safe use, and an implementation system.

In accordance with section 505-1(g)(4)(B) of the FD&C Act, we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

**Elements to Assure Safe Use:** We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will reduce the burden on the healthcare delivery system of complying with the REMS.

**Elements to Assure Safe Use:** Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of

U.S. Food & Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20903  
[www.fda.gov](http://www.fda.gov)

DEAR059

2021 REMS 001808

serious complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers who prescribe the drugs have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the ETASU (as outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your ANDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B) of the FD&C Act, you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A) of the FD&C Act.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR AND A 091178/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

**AND A 091178/S-000  
PROPOSED REMS MODIFICATION-AMENDMENT**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

**SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email [REMS\\_Website@fda.hhs.gov](mailto:REMS_Website@fda.hhs.gov).

If you have any questions, call

(b)(6)/PPI

.

Sincerely,

*{See appended electronic signature page}*

(b)(6)/PPI

Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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(b)(6)/PPI

12/16/2021 03:21:22 PM

DEAR062

2021 REMS 001811

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES</b> Food and Drug Administration <b>APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE</b> <i>(Title 21, Code of Federal Regulations, Parts 314 &amp; 601)</i>		Form Approved: OMB No. 0910-0338 Expiration Date: March 31, 2020 See PRA Statement on page 3. 1. Date of Submission (mm/dd/yyyy) 06/22/2022	
<b>APPLICANT INFORMATION</b>		2. Name of Applicant Danco Laboratories, LLC	
3. Telephone Number (Include country code if applicable and area code) 877-432-7596		4. Facsimile (FAX) Number (Include country code if applicable and area code) (b)(4)/TS-CI; (b)(6)/PPI	
5. Applicant Address			
Address 1 (Street address, P.O. box, company name c/o) P.O. Box 4816 Address 2 (Apartment, suite, unit, building, floor, etc.) City New York State/Province/Region NY Country USA ZIP or Postal Code 10185		Email Address (b)(4)/TS-CI; (b)(6)/PPI Applicant DUNS 005078048 U.S. License Number if previously issued	
6. Authorized U.S. Agent (Required for non-U.S. applicants)			
Authorized U.S. Agent Name Address 1 (Street address, P.O. box, company name c/o) Address 2 (Apartment, suite, unit, building, floor, etc.) City State ZIP Code		Telephone Number (Include area code) FAX Number (Include area code) Email Address U.S. Agent DUNS	
<b>PRODUCT DESCRIPTION</b>		7. NDA, ANDA, or BLA Application Number 020687	
8. Supplement Number (If applicable) 025		9. Established Name (e.g., proper name, USP/USAN name) Mifepristone	
10. Proprietary Name (Trade Name) (If any) Mifeprex			
11. Chemical/Biochemical/Blood Product Name (If any) 11β-[p-(dimethylamino)phenyl]-17β-hydroxy-17-(1-propynyl)estra-4, 9-dien-3-one			
12. Dosage Form Tablet		13. Strengths 200 mg	
14. Route of Administration Oral		15A. Proposed Indication for Use Medical Termination of Intrauterine Pregnancy	
Is this indication for a rare disease (prevalence <200,000 in U.S.)? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		Does this product have an FDA Orphan Designation for this indication? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
If yes, provide the Orphan Designation number for this indication:		Continuation Page for #15	
15B. SNOMED CT Indication Disease Term (Use continuation page for each additional indication and respective coded disease term) 386639001  Termination of pregnancy (procedure)			
<b>APPLICATION INFORMATION</b>		16. Application Type (Select one) <input checked="" type="checkbox"/> New Drug Application (NDA) <input type="checkbox"/> Biologics License Application (BLA) <input type="checkbox"/> Abbreviated New Drug Application (ANDA)	
17. If an NDA, identify the type <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		18. If a BLA, identify the type <input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)	
19. If a 351(k), identify the biological reference product that is the basis for the submission. Name of Biologic: _____ Holder of Licensed Application: _____			
20. If an ANDA, or 505(b)(2), identify the listed drug product that is/are the basis for the submission. Name of Drug: _____ Application Number of Relied Upon Product: _____			
Indicate Patent Certification: <input type="checkbox"/> P1 <input type="checkbox"/> P2 <input type="checkbox"/> P3 <input type="checkbox"/> P4 <input type="checkbox"/> Section viii - MOU <input type="checkbox"/> Statement of no relevant patents			

21. Submission (See instructions) <input type="checkbox"/> Original <input type="checkbox"/> Labeling Supplement <input type="checkbox"/> CMC Supplement <input type="checkbox"/> Efficacy Supplement <input type="checkbox"/> Annual Report <input type="checkbox"/> Product Correspondence <input checked="" type="checkbox"/> REMS Supplement <input type="checkbox"/> Postmarketing Requirements or Commitments <input type="checkbox"/> Periodic Safety Report <input type="checkbox"/> Request for Proprietary Name Review <input type="checkbox"/> Other (Specify): _____		
22. Submission Sub-Type <input type="checkbox"/> Presubmission <input type="checkbox"/> Amendment <input checked="" type="checkbox"/> Initial Submission <input type="checkbox"/> Resubmission	23. If a supplement, identify the appropriate category. <input type="checkbox"/> CBE <input checked="" type="checkbox"/> Prior Approval (PA) <input type="checkbox"/> CBE-30	
24. For Originals and all Supplements, is the product a combination product (21 CFR 3.2(e))? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Combination Product Type (See instructions)	Request for Designation (RFD) Number
25. Does the submission contain: Only Pediatric data? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Human factors information? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	26. Proposed Marketing Status (Select one) <input checked="" type="checkbox"/> Prescription Product (Rx) <input type="checkbox"/> Over-The-Counter Product (OTC)
27. Reasons for Submission Proposed Major SSS REMS Program Modification		
28. Establishment Information (Full establishment information should be provided in the body of the application.)		
Establishment Name		
Address 1 (Street address, P.O. box, company name c/o)		Registration (FEI) Number
Address 2 (Apartment, suite, unit, building, floor, etc.)		MF Number
City	State/Province/Region	Establishment DUNS Number
Country	ZIP or Postal Code	
Is the establishment new to the application? <input type="checkbox"/> Yes <input type="checkbox"/> No		What is the status of the establishment? <input type="checkbox"/> Pending <input type="checkbox"/> Active <input type="checkbox"/> Inactive <input type="checkbox"/> Withdrawn
Establishment Contact Information at the site/facility		
Name of Contact for the Establishment		Telephone Number (Include area code)
Address 1 (Street address, P.O. box, company name c/o)		FAX Number (Include area code)
Address 2 (Apartment, suite, unit, building, floor, etc.)		Email Address
City	State/Province/Region	
Country	ZIP or Postal Code	
Manufacturing Steps and/or Type of Testing		Is the site ready for inspection? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A If No, when will site be ready? (mm/dd/yyyy) _____
		Continuation Page for #28
29. Cross References (List related BLAs, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, MAFs, and DMFs referenced in the current application.) N/A		
30. This application contains the following items (Select all that apply)		
<input type="checkbox"/> 1. Index	<input checked="" type="checkbox"/> 2. Labeling (Select one): <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	<input type="checkbox"/> 3. Summary (21 CFR 314.50 (c))
<input type="checkbox"/> 4. Chemistry Section <input type="checkbox"/> A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) <input type="checkbox"/> B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) <input type="checkbox"/> C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)		
<input type="checkbox"/> 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)		<input type="checkbox"/> 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
<input type="checkbox"/> 7. Clinical microbiology section (e.g., 21 CFR 314.50(d)(4))		<input type="checkbox"/> 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)

Item 30 continued on page 3

30. This application contains the following items (Continued; select all that apply)

<input type="checkbox"/> 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	<input type="checkbox"/> 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
<input type="checkbox"/> 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	<input type="checkbox"/> 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
<input type="checkbox"/> 13. Patent information on any patent that claims the drug/biologic (21 U.S.C. 355(b) or (c))	<input type="checkbox"/> 14. A patent certification with respect to any patent that claims the drug/biologic (21 U.S.C. 355 (b)(2) or (j)(2)(A))
<input type="checkbox"/> 15. Establishment description (21 CFR Part 600, if applicable)	<input type="checkbox"/> 16. Debarment certification (FD&C Act 306 (k)(1))
<input type="checkbox"/> 17. Field copy certification (21 CFR 314.50 (l)(3))	<input type="checkbox"/> 18. User Fee Cover Sheet (PDUFA Form FDA 3397, GDUFA Form FDA 3794, BsUFA Form FDA 3792, or MDUFA Form FDA 3601)
<input type="checkbox"/> 19. Financial Disclosure Information (21 CFR Part 54)	
<input checked="" type="checkbox"/> 20. Other (Specify): <u>Proposed Major SSS REMS Program Modification</u>	

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to, the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state, and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.

**Warning:** A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

31. Typed Name and Title of Applicant's Responsible Official (b)(4)/TS-CI; (b)(6)/PPI		32. Date (mm/dd/yyyy) 06/22/2022
33. Telephone Number (Include country code if applicable and area code) 877-432-7596	34. FAX Number (Include country code if applicable and area code) (b)(4)/TS-CI; (b)(6)/PPI	35. Email Address (b)(4)/TS-CI; (b)(6)/PPI
36. Address of Applicant's Responsible Official		
Address 1 (Street address, P.O. box, company name c/o) P.O. Box 4816		
Address 2 (Apartment, suite, unit, building, floor, etc.)		
City New York	State/Province/Region NY	
Country USA	ZIP or Postal Code 10185	
37. Signature of Applicant's Responsible Official or Other Authorized Official (b)(4)/TS-CI; (b)(6)/PPI	<b>Sign</b>	38. Countersignature of Authorized U.S. Agent <b>Sign</b>

**The information below applies only to requirements of the Paperwork Reduction Act of 1995.**

The burden time for this collection of information is estimated to average 24 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
Office of Operations  
Paperwork Reduction Act (PRA) Staff  
PRASStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

**DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF EMAIL ADDRESS.**

CONFIDENTIAL\*

## Danco Laboratories, LLC

P.O. Box 4816, New York,  
New York 10185  
Tel: (b)(4)/TS-CI; (b)(6)/  
Facsimile: (b)(4)/TS-CI; (b)(6)/  
PPI

### NEW SUPPLEMENT FOR NDA 020687/S-025 PRIOR APPROVAL SUPPLEMENT PROPOSED MAJOR REMS MODIFICATION

June 22, 2022

(b)(6)/PPI

Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705

Re: NDA 020687, eCTD Sequence No.18  
MIFEPREX® (mifepristone) tablets, 200 mg

#### PRIOR APPROVAL SUPPLEMENT S-025

#### PROPOSED MAJOR SSS REMS PROGRAM MODIFICATION INCLUDING CHANGES TO LABELING AND MEDICATION GUIDE

Dear (b)(6)/PPI

This prior approval supplement S-025 is being submitted by Danco Laboratories, LLC in response to FDA's [REMS Modification Notification dated December 16, 2021](#). This supplement addresses FDA's determination that the approved Mifepristone Single Shared System Risk Evaluation and Mitigation Strategy ("SSS REMS") must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

Danco and GenBioPro have worked collaboratively to modify the SSS REMS to include the necessary elements to assure safe use of mifepristone. GenBioPro, Inc. will be submitting identical documents to their ANDA 091178, adjusted for company name and other proprietary information.

The proposed major modifications to the SSS REMS were developed based on the recommendations provided by FDA in the REMS Modification Notification as well as feedback received in the Type A Meeting Written Response communication dated [April 08, 2022](#) ("[Written Response](#)"). Additionally, the Full Prescribing Information and the Medication Guide have been

\* This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Applicant requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45.

revised to align with the modifications to the SSS REMS. All revised documents include gender neutral adjustments where indicated.

The below list of documents are included in this submission.

Documents Provided in this Submission	eCTD Location
<p>Summary of Modifications</p> <p><u>Summary of Modifications to Mifepristone SSS REMS – PDF</u></p> <p><u>Summary of Modifications to Mifepristone SSS REMS – MS Word</u></p>	<p><a href="#">1.16.2.2</a></p> <p><a href="#">1.16.2.2</a></p>
<p>Mifepristone SSS REMS Proposed Modification</p> <p><u>Mifepristone SSS REMS Modification – TRACK CHANGES MS Word Version</u></p> <p><u>Mifepristone SSS REMS Modification – CLEAN MS Word Version</u></p> <p><u>Side-by-Side Comparison of the SSS REMS Modification and REMS Materials with the Current SSS REMS and REMS Materials</u></p>	<p><a href="#">1.16.2.2</a></p> <p><a href="#">1.16.2.2</a></p> <p><a href="#">1.16.2.2</a></p>
<p>Revised Patient Agreement</p> <p><u>Revised Patient Agreement –TRACK CHANGES MS Word version</u></p> <p><u>Revised Patient Agreement – CLEAN MS Word version</u></p>	<p><a href="#">1.16.2.2</a></p> <p><a href="#">1.16.2.2</a></p>
<p>Revised Prescriber Agreement</p> <p><u>Revised Danco Prescriber Agreement –TRACK CHANGES MS Word version</u></p> <p><u>Revised Danco Prescriber Agreement –CLEAN MS Word version</u></p>	<p><a href="#">1.16.2.2</a></p> <p><a href="#">1.16.2.2</a></p>
<p>New Proposed Pharmacy Agreement</p> <p><u>New Proposed Danco Pharmacy Agreement – MS Word</u></p>	<p><a href="#">1.16.2.2</a></p>

\* This document constitutes trade secret and confidential commercial information exempt from public disclosure under **21 C.F.R. 20.61**. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Applicant requests immediate notification and an opportunity for consultation in accordance with **21 C.F.R. 20.45**.


**CONFIDENTIAL\***

Documents Provided in this Submission	eCTD Location
Revised REMS Supporting Document  <u>REMS Supporting Document –TRACK CHANGES MS Word version</u>  <u>REMS Supporting Document – CLEAN MS Word version</u>	  <a href="#"><u>1.16.2.2</u></a>  <a href="#"><u>1.16.2.2</u></a>
Revised Full Prescribing Information and Medication Guide  <u>Revised Danco Full Prescribing Information and Medication Guide– Redline Annotated MS Word version</u>  <u>Revised Danco Full Prescribing Information and Medication Guide– Clean MS Word version</u>	  <a href="#"><u>1.14.1.2</u></a>  <a href="#"><u>1.14.1.2</u></a>

Please contact me with any questions or if you need additional information.

Sincerely,

(b)(4)/TS-CI; (b)(6)/PPI



\* This document constitutes trade secret and confidential commercial information exempt from public disclosure under **21 C.F.R. 20.61**. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Applicant requests immediate notification and an opportunity for consultation in accordance with **21 C.F.R. 20.45**.

**DEAR068**

2023 SUPP 000262

**ELECTRONIC SUBMISSION SPECIFICATIONS**

<b>Root Folder Name:</b>	nda020687
<b>eCTD Sequence Number:</b>	0018
<b>Size of Submission:</b>	Approximately 6 MB
<b>No. Files:</b>	24
<b>No. Folders:</b>	12
<b>Virus Protection Statement:</b>	This submission is virus free
<b>Anti-Virus Software Information:</b>	Microsoft Antimalware for Azure (eCTD Server)



NDA 020687

**MEETING REQUEST-  
WRITTEN RESPONSES**

Danco Laboratories, LLC

(b)(4)/TS-CI; (b)(6)/PPI

P.O. Box 4816  
New York, NY 10185

Dear (b)(4)/TS-CI; (b)(6)/PPI

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mifeprex (mifepristone) Tablets.

We also refer to your submission dated March 11, 2022, containing a meeting request. The purpose of the requested meeting was to discuss the proposed modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg, the REMS materials, and other supporting documents to facilitate a submission by April 15, 2022.

Further reference is made to our Meeting Granted letter dated March 16, 2022, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your March 11, 2022, background package.

If you have any questions,

(b)(6)/PPI

Sincerely,

*{See appended electronic signature page}*

(b)(6)/PPI

Center for Drug Evaluation and Research

Enclosure:

- Written Responses

**DEAR070**

2023 SUPP 000264

NDA 020687

Page 2

## WRITTEN RESPONSES

**Meeting Type:** Type A  
**Meeting Category:** Post-Action Meeting, REMS

**Application Number:** 020687

**Product Name:** Mifeprex (mifepristone) Tablets

**Indication:** Mifepristone, in a regimen with misoprostol, is indicated for the medical termination of intrauterine pregnancy through 70 days gestation

**Applicant Name:** Danco Laboratories, LLC

## BACKGROUND

On December 16, 2021, FDA issued a letter to notify the applicants of mifepristone for medical termination of early pregnancy that the single, shared system REMS must be modified as follows:

**Elements to Assure Safe Use:** FDA determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will also minimize the burden on the healthcare delivery system of complying with the REMS.

**Elements to Assure Safe Use:** Pursuant to 505-1(f)(1), FDA also determined that an additional element to assure safe use is necessary to mitigate the risk of serious complications associated with mifepristone listed in the labeling of the drug. Modification of the REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

NDA 020687

Page 3

## QUESTIONS AND RESPONSES

### Question 1: For pharmacies that will dispense mifepristone:

**Question 1 a):** Will the Agency accept a certification process and requirements that are the same for pharmacies dispensing by mail or local courier and pharmacies dispensing in-person to the patient?

**FDA Response:** *You may propose the same certification for different pharmacy dispensing models. However, we may need additional information on your proposal depending on your dispensing model. A review of your proposed REMS modifications will be necessary to determine if your overall proposal for pharmacy certification assures the safe use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.*

**Question 1 b):** Is certification of an authorized representative of the pharmacy on behalf of all of its multiple locations and personnel acceptable to the Agency for the revised mifepristone REMS?

**FDA Response:** *Yes, a pharmacy can designate an authorized representative to carry out the certification process regardless of whether that pharmacy has one location or multiple locations. Note that the authorized representative is responsible for and must agree to oversee implementation of and compliance with the Mifepristone REMS Program. In addition, as part of your proposed implementation system, you must have a process to ensure that the pharmacies distributing mifepristone comply with the Mifepristone REMS Program requirements for certified pharmacies. In your submission, describe how you would implement and monitor compliance by certified pharmacies with the Mifepristone REMS Program requirements.*

**Question 1 c):** Would FDA consider approving Pharmacy Certification with the following requirements and advise on other elements that also need to be addressed?

Requirements: The pharmacy, through its authorized representative, certifies that it will implement necessary actions to ensure the following:

- (i) Dispense mifepristone only under prescriptions issued by (b)(4)/TS-CI a certified prescriber (see below for contemplated verification and questions on certified prescribers);
- (ii) No transfer of mifepristone other than to a patient per above, a certified prescriber, another certified pharmacy, or for returns or destruction;
- (iii) Communicate any reported deaths of mifepristone users to the prescriber;

NDA 020687

Page 4

- (iv) The Medication Guide is available to patients;
- (v) Maintain records of the above and accept audits; and
- (vi) Protect the confidentiality and privacy of providers and patients.

***FDA Response:*** *Specifics on pharmacy requirements will be a matter of FDA review. At this time, we have insufficient information regarding permitting mifepristone to be transferred from one certified pharmacy to another certified pharmacy or from a certified pharmacy to a certified prescriber. In your submission, provide your rationale and examples of when and how such a transfer would occur. We encourage you to review the Format and Content of a REMS Document Guidance for Industry which can be found at Format and Content of a REMS Document Guidance for Industry | FDA.*

*In general, we agree with your proposal for (iii), (iv), (v), and (vi) but specific details will be a review issue. See our response to question 1 d) for (i).*

**Question 1 d):** As the Agency understands, providing medical abortion with mifepristone may expose prescribers to extreme risks to their safety that are different from any other drug product. The ever-present risk of anti-abortion violence creates material security and confidentiality risks for mifepristone prescribers, distributors, pharmacies, and patients. Accordingly, care must be taken to ensure that any modification to the Mifepristone REMS Program does not create a risk of unauthorized disclosure of identifying information about any of these stakeholders. (b)(4)/TS-CI

. Any apparent or potential risk would cause many prescribers—including existing prescribers—to refrain from becoming or remaining mifepristone prescribers.

Nonetheless, the Sponsors assume that, if mifepristone is to be dispensed by pharmacies, the REMS must include a process by which a pharmacy first confirms that the prescriber is specially certified. Currently the prescriber verification process is handled by the distributors for each product, each of which receives a Prescriber Agreement and distributes product only on the basis of a valid order from a certified prescriber. The number of distributors and prescribers is quite small; however, the nature and size of a prescriber certification system for dispensing pharmacies present potential disclosure risk of an entirely different magnitude. (b)(4)/TS-CI

In short, the critical elements of an effective system must reconcile prescriber security and confidentiality, while providing reasonable

NDA 020687

Page 5

assurance that pharmacies dispense only in response to a valid prescription from a specially certified prescriber.

With that in mind, would the Agency consider or comment on a verification system that includes the following elements:

(i)

(b)(4)/TS-CI

(ii) The pharmacy must keep prescription records.

**FDA Response:** *The verification process for safe use conditions by the pharmacy is a matter of FDA review.*

(b)(4)/TS-CI

*In your submission, specify how you would implement and monitor compliance with this requirement.*

**Question 2:** In accordance with the Mifepristone REMS Program, medical assessment, counseling, and follow-up are carried out by healthcare professionals and qualified persons acting under the supervision of the certified prescriber responsible for assuring compliance with required procedures. To eliminate confusion for healthcare providers, this should be expressly recognized as an acceptable approach for mifepristone prescribing under the REMS.

Accordingly, would FDA consider or accept an explicit clarification to the REMS that prescriber certification establishes the certification of the prescriber and the healthcare providers who are working by or under their supervision?





**FDA Response:** *Yes. The Prescriber Agreement Form could be revised for the certified prescriber to stipulate that assessment, counseling, prescribing, and follow-up may be conducted by the certified prescriber and health care providers who are working under the supervision of the certified prescriber. Propose specific edits to the Prescriber Agreement Form to address this issue.*

**Question 3:**

(b)(4)/TS-CI

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Page 6

(b)(4)/TS-CI  
**FDA Response:**(b)(4)/TS-CI  
**Question 4:**(b)(4)/TS-CI  
  
**FDA Response:**(b)(4)/TS-CI  


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/s/  
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(b)(6)/PPI

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

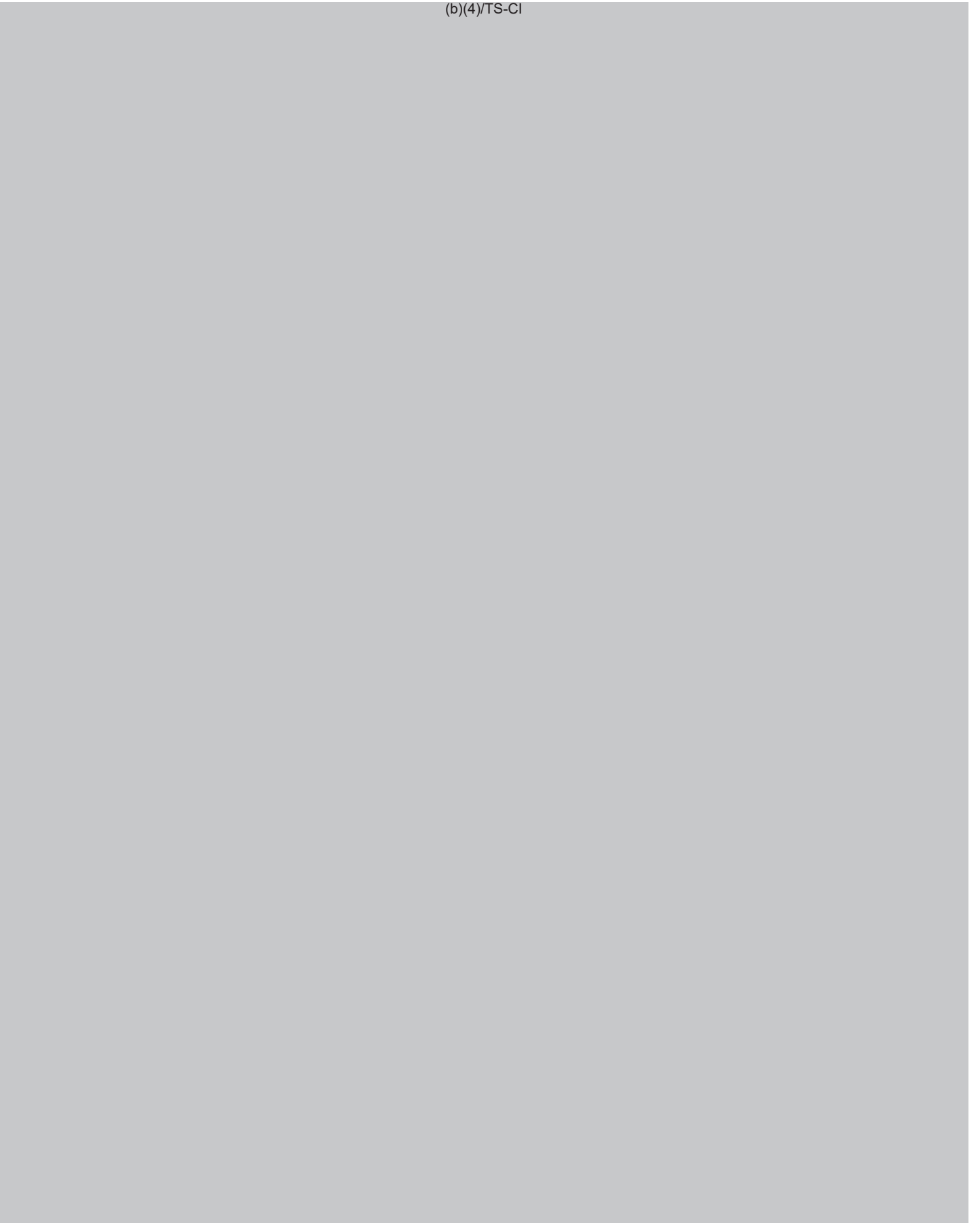
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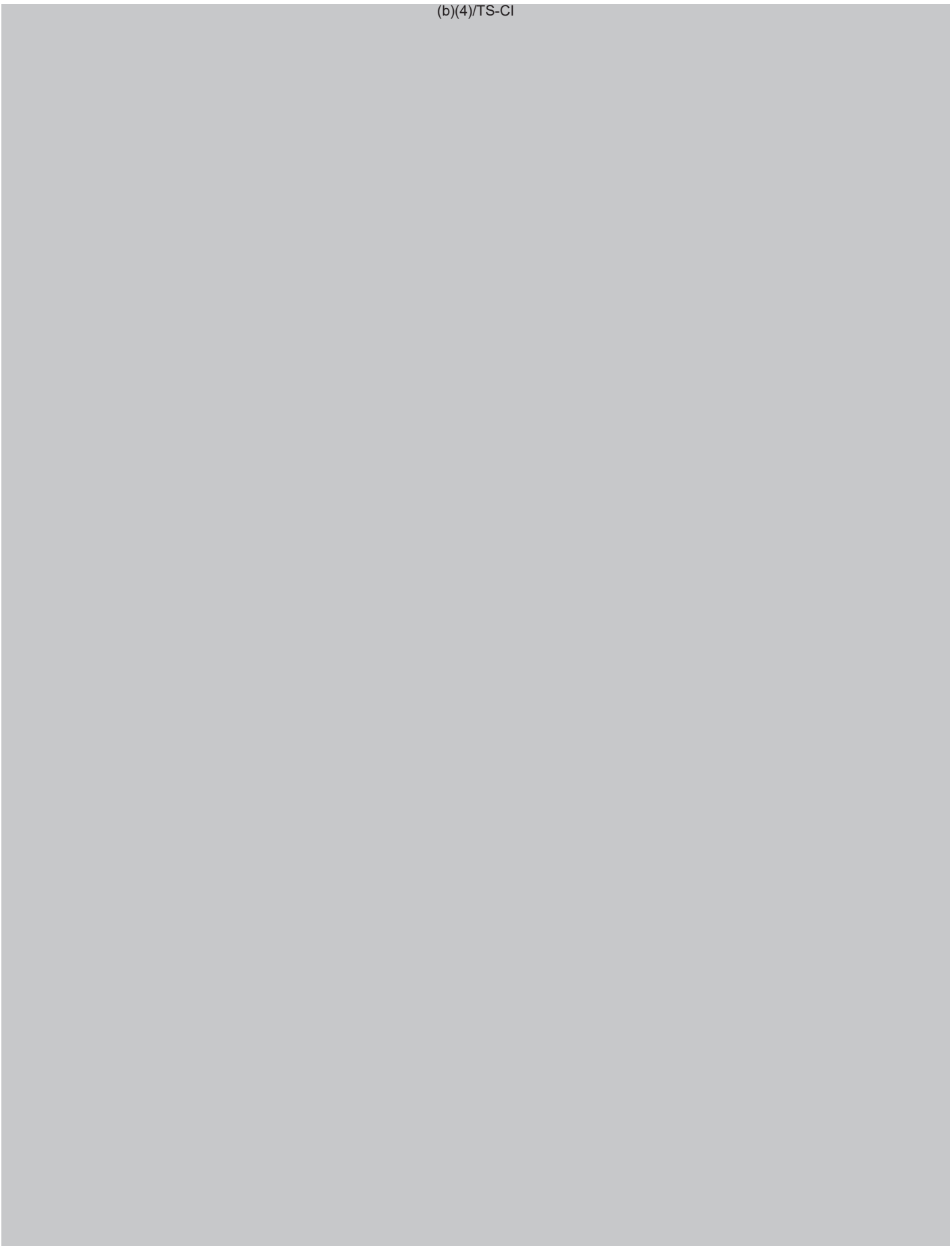
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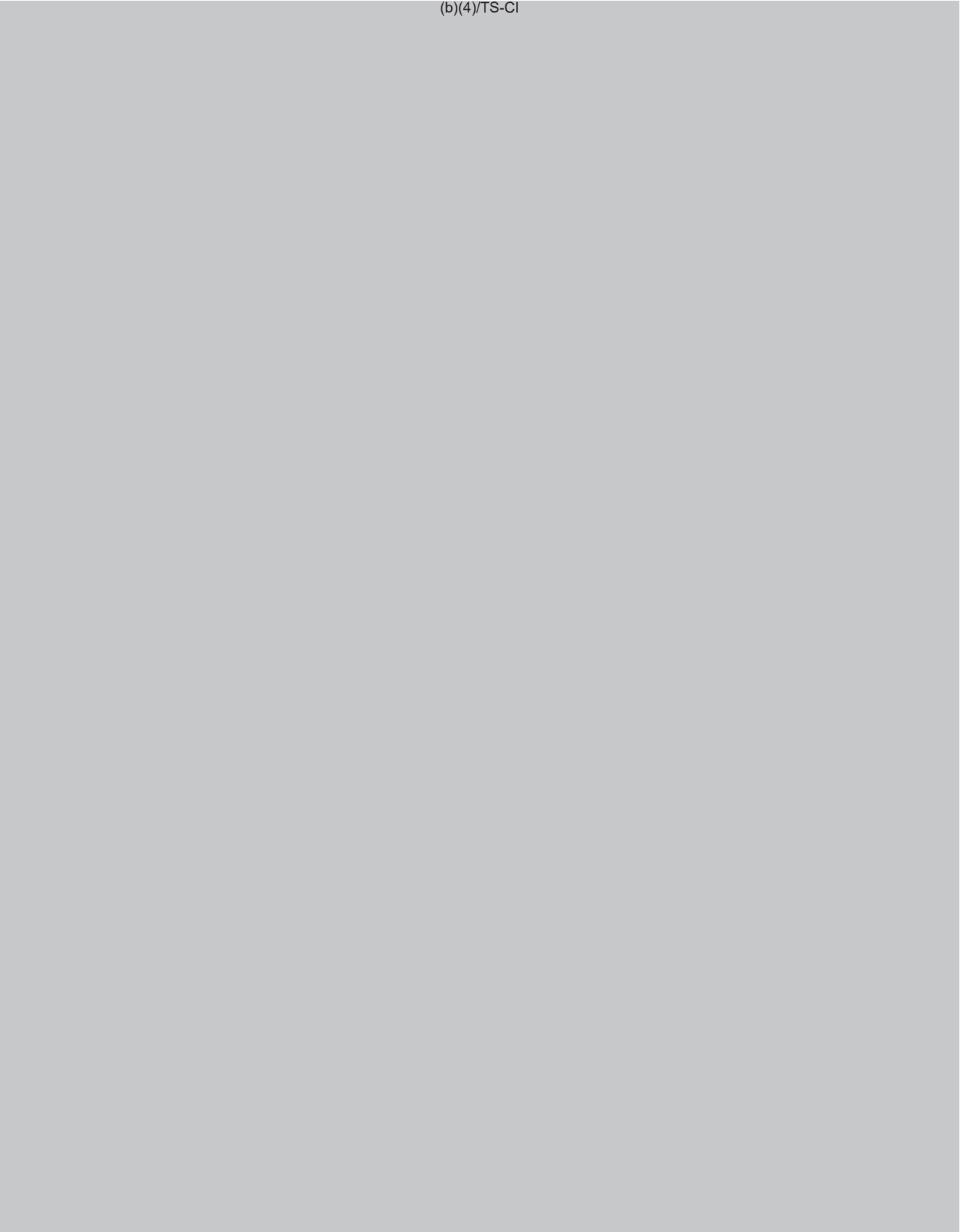
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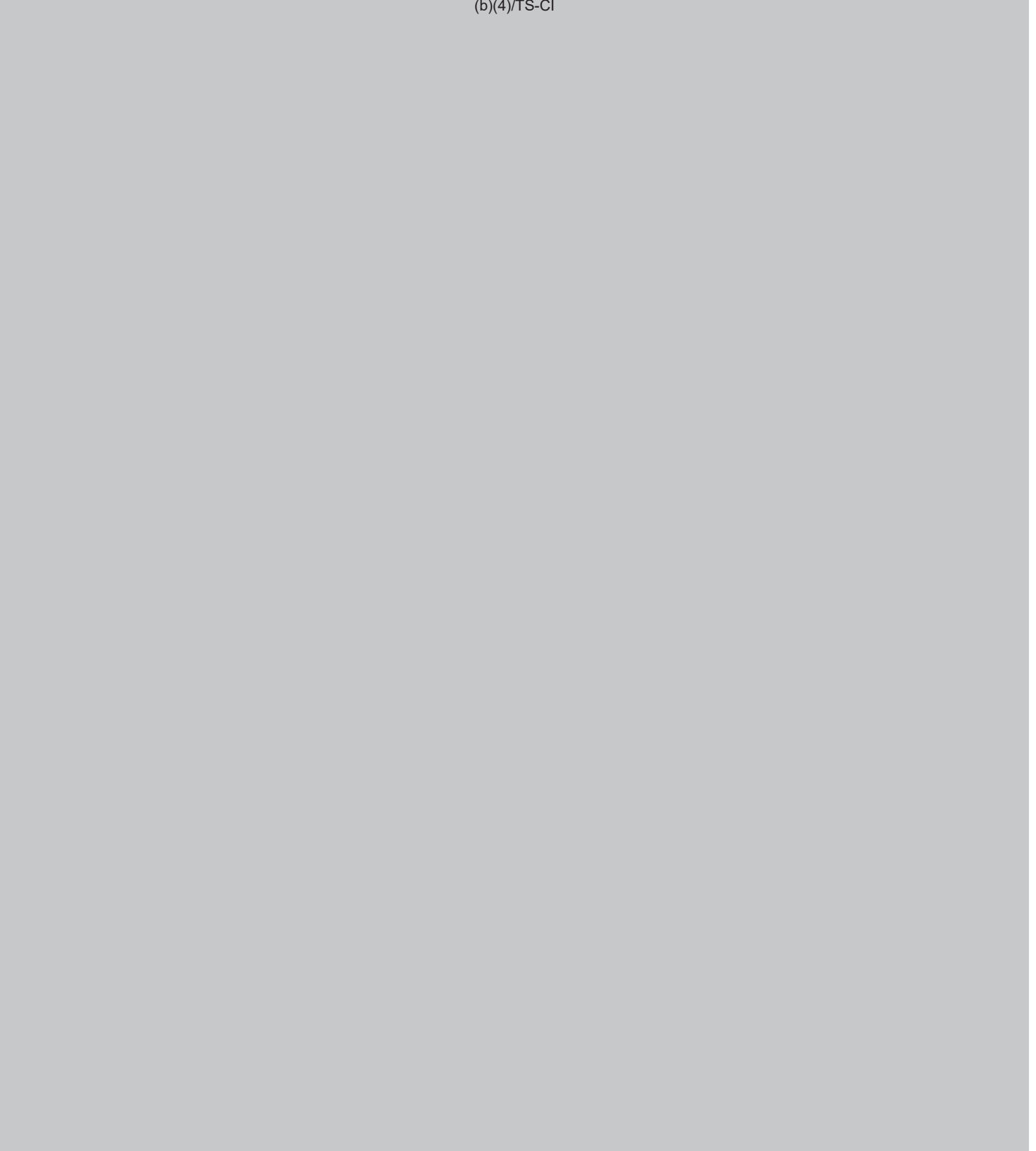
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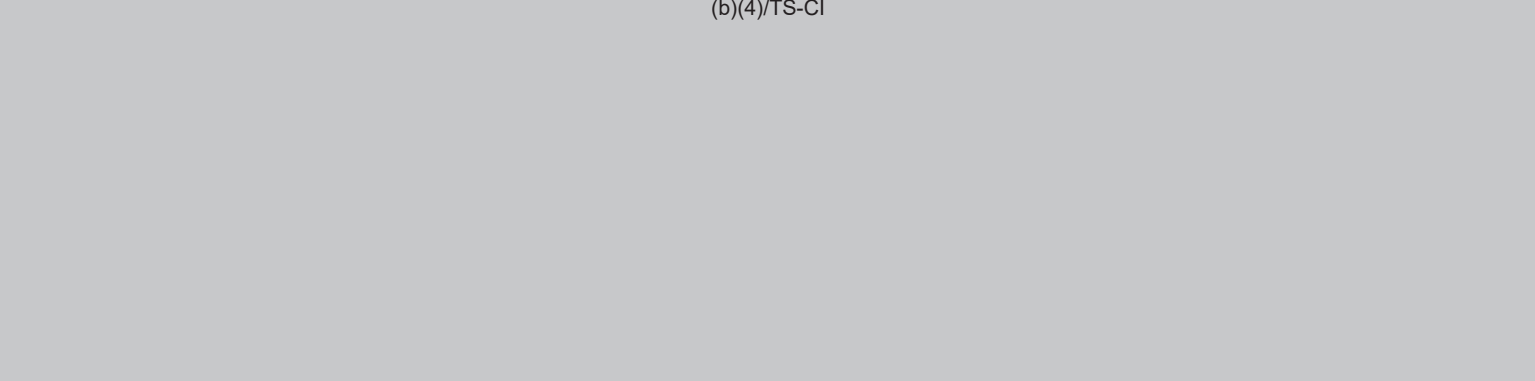
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(b)(4)/TS-CI



**MEDICATION GUIDE**

(b)(4)/TS-CI




(b)(4)/TS-CI



(b)(4)/TS-CI




(b)(4)/TS-CI



PATIENT AGREEMENT FORM

Mifepristone Tablets, 200mg

(b)(4)/TS-CI



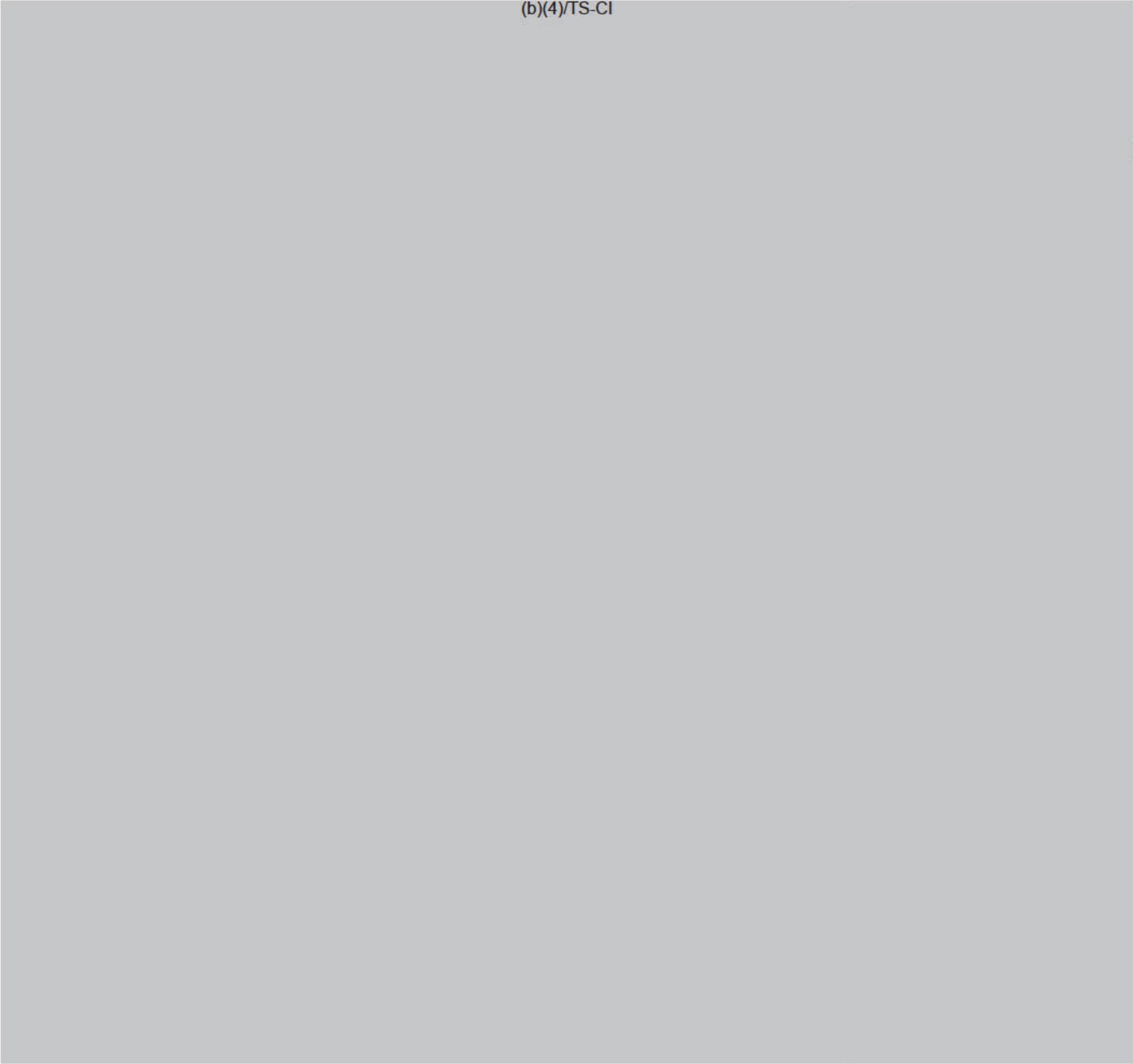
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MIFEPREX®  
(Mifepristone) Tablets, 200 mg

**Prescriber Agreement Form**

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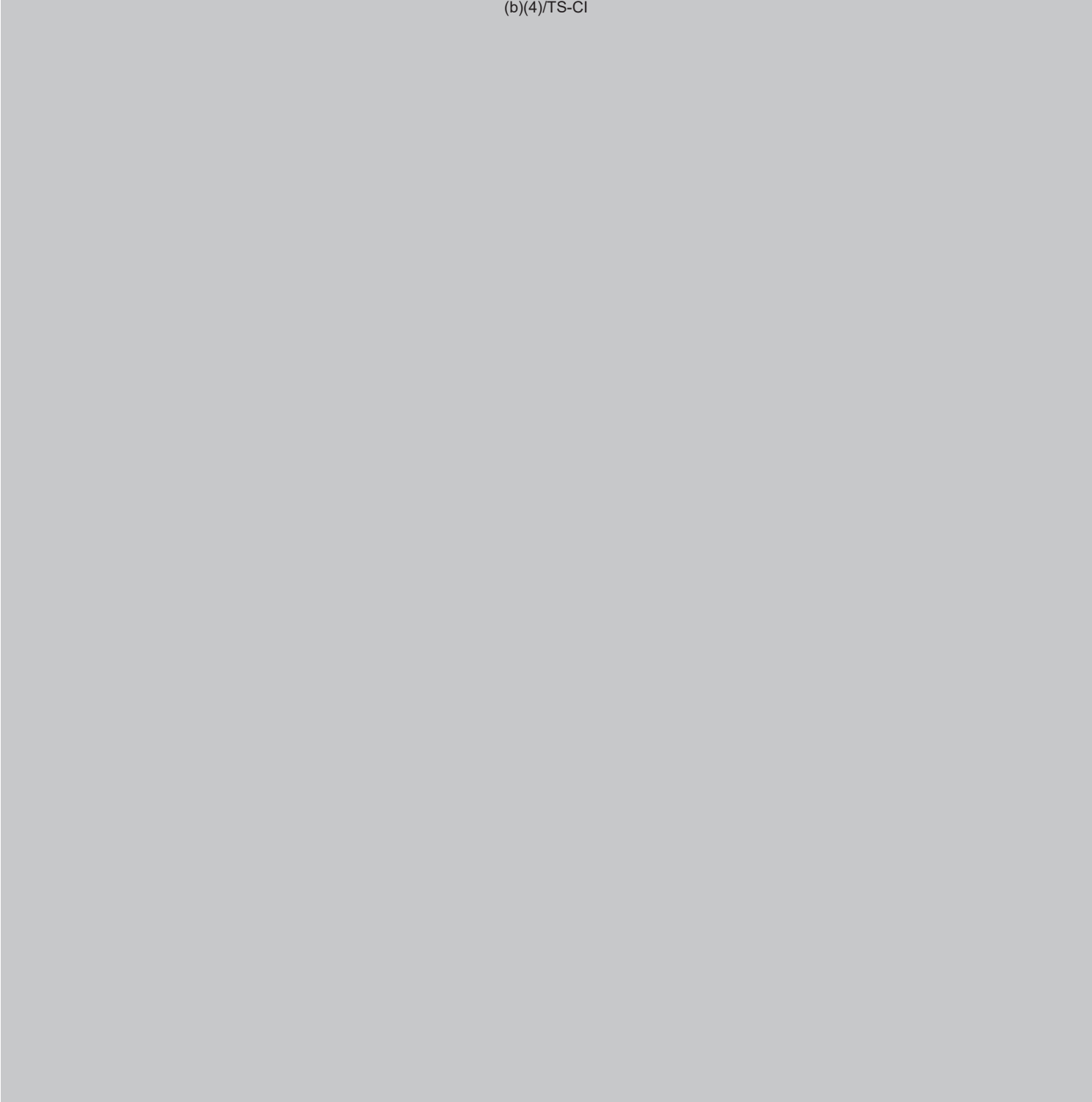


APPEARS THIS WAY ON ORIGINAL

M I F E P R E X<sup>®</sup>  
(Mifepristone) Tablets, 200 mg

**PHARMACY AGREEMENT FORM**

(b)(4)/TS-CI



(b)(4)/TS-CI





NDA 020687

## REMS MODIFICATION NOTIFICATION

Danco Laboratories, LLC

(b)(4)/TS-CI; (b)(6)/PPI

P.O. Box 4816  
New York, NY 10185

Dear (b)(4)/TS-CI; (b)(6)/PPI

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

The REMS for mifepristone was originally approved on June 8, 2011, and your single shared system REMS (SSS REMS) was approved on April 11, 2019. Your last SSS REMS modification was approved May 14, 2021. The SSS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

**Elements to Assure Safe Use:** We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will also minimize the burden on the healthcare delivery system of complying with the REMS.

**Elements to Assure Safe Use:** Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of serious

NDA 020687

Page 2

complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe use conditions.

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS must include a timetable for submission of assessments. The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS, and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your NDA.

NDA 020687

Page 3

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR NDA 020687/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 020687/S-000  
PROPOSED REMS MODIFICATION-AMENDMENT**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

**SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email [FDAREMSwebsite@fda.hhs.gov](mailto:FDAREMSwebsite@fda.hhs.gov).

NDA 020687

Page 4

If you have any questions, call

(b)(6)/PPI

Sincerely,

*{See appended electronic signature page}*

(b)(6)/PPI

Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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(b)(6)/PPI

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(b)(4)/TS-CI

Mifepristone Tablets, 200 mg

Progestin Antagonist

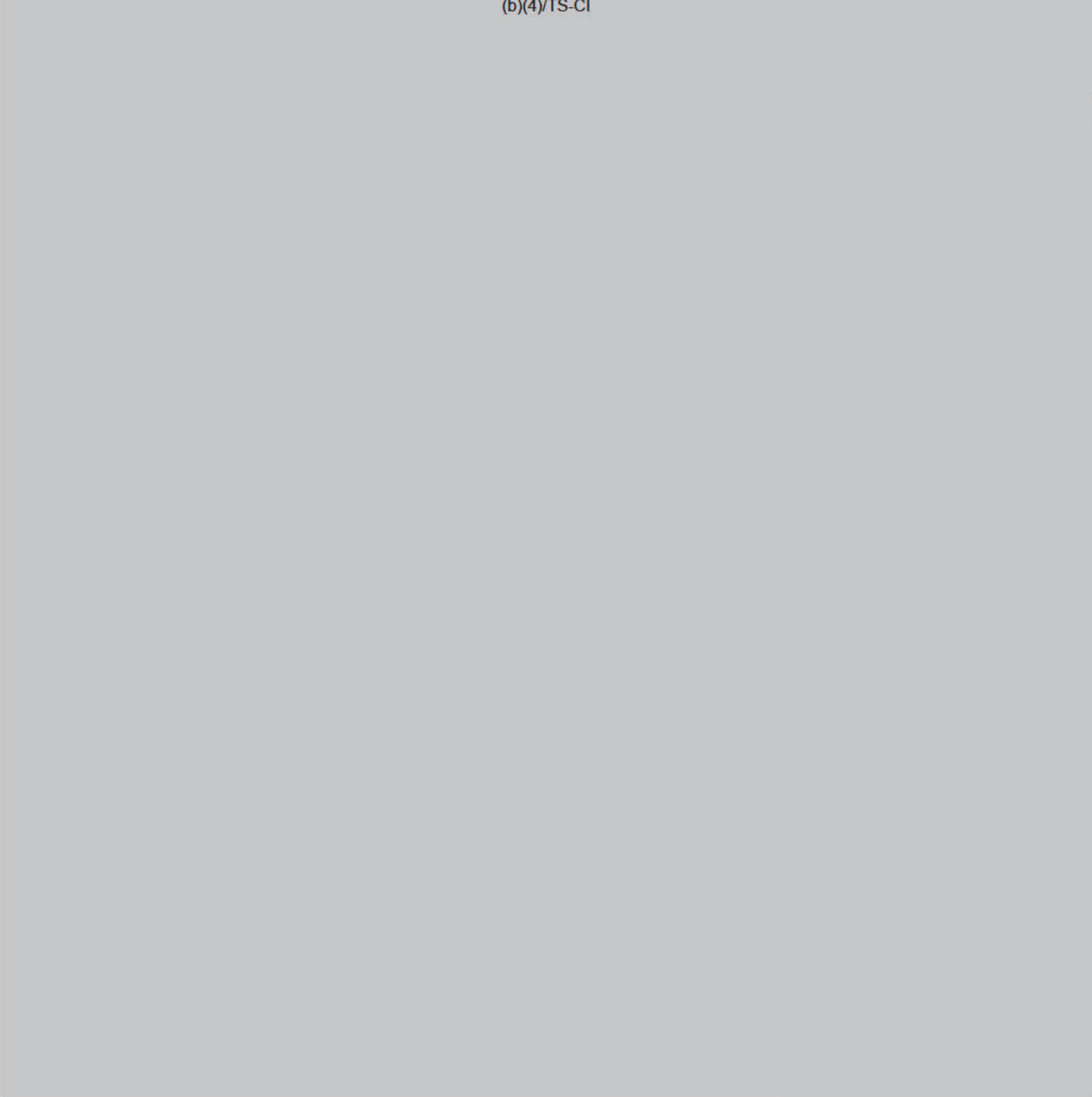
**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200MG**

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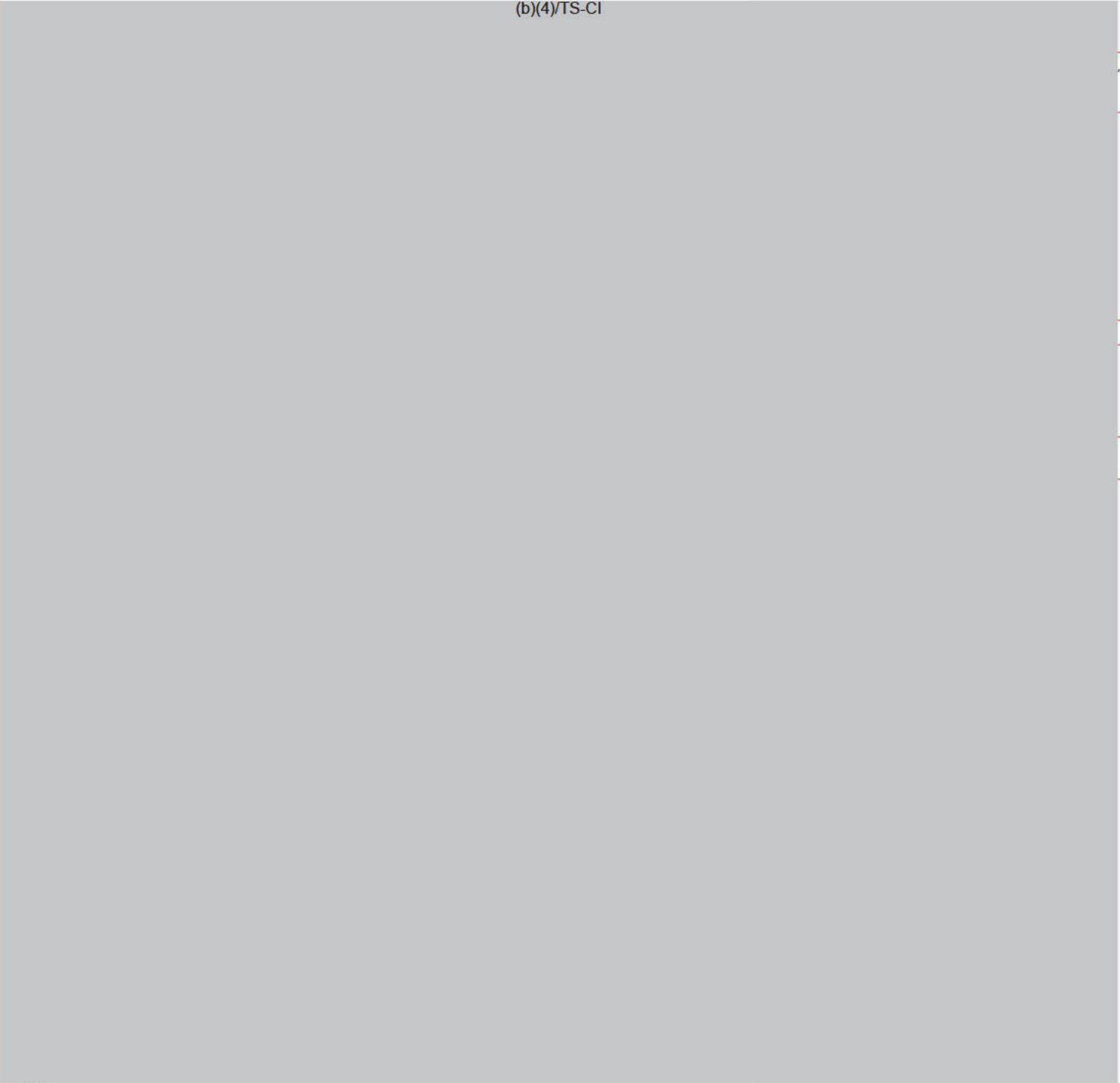
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Reference D: 4499499

**Mifepristone Tablets, 200 mg<sup>1</sup>****SINGLE SHARED SYSTEM RISK EVALUATION AND MITIGATION STRATEGY  
(REMS) SUPPORTING DOCUMENT**

(b)(4)/TS-CI

<sup>1</sup> This document constitutes trade secret and confidential information exempt from public disclosure under 21 C.F.R. § 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, the Sponsors request immediate notification and an opportunity for consultation in accordance with 21 C.F.R. § 20.45.

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Confidential

(b)(4)/TS-CI



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**DEAR115**

2023 SUPP 000309

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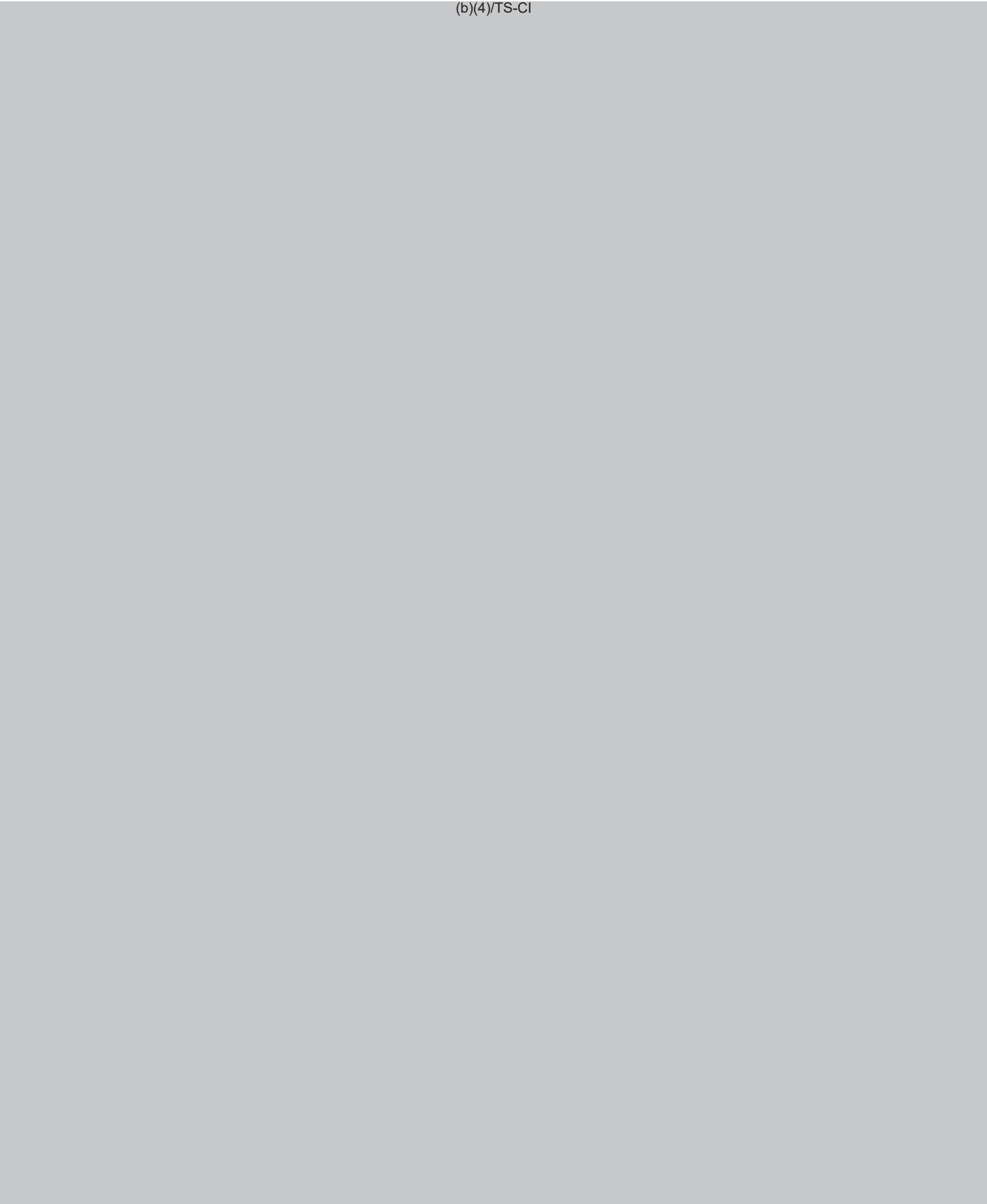
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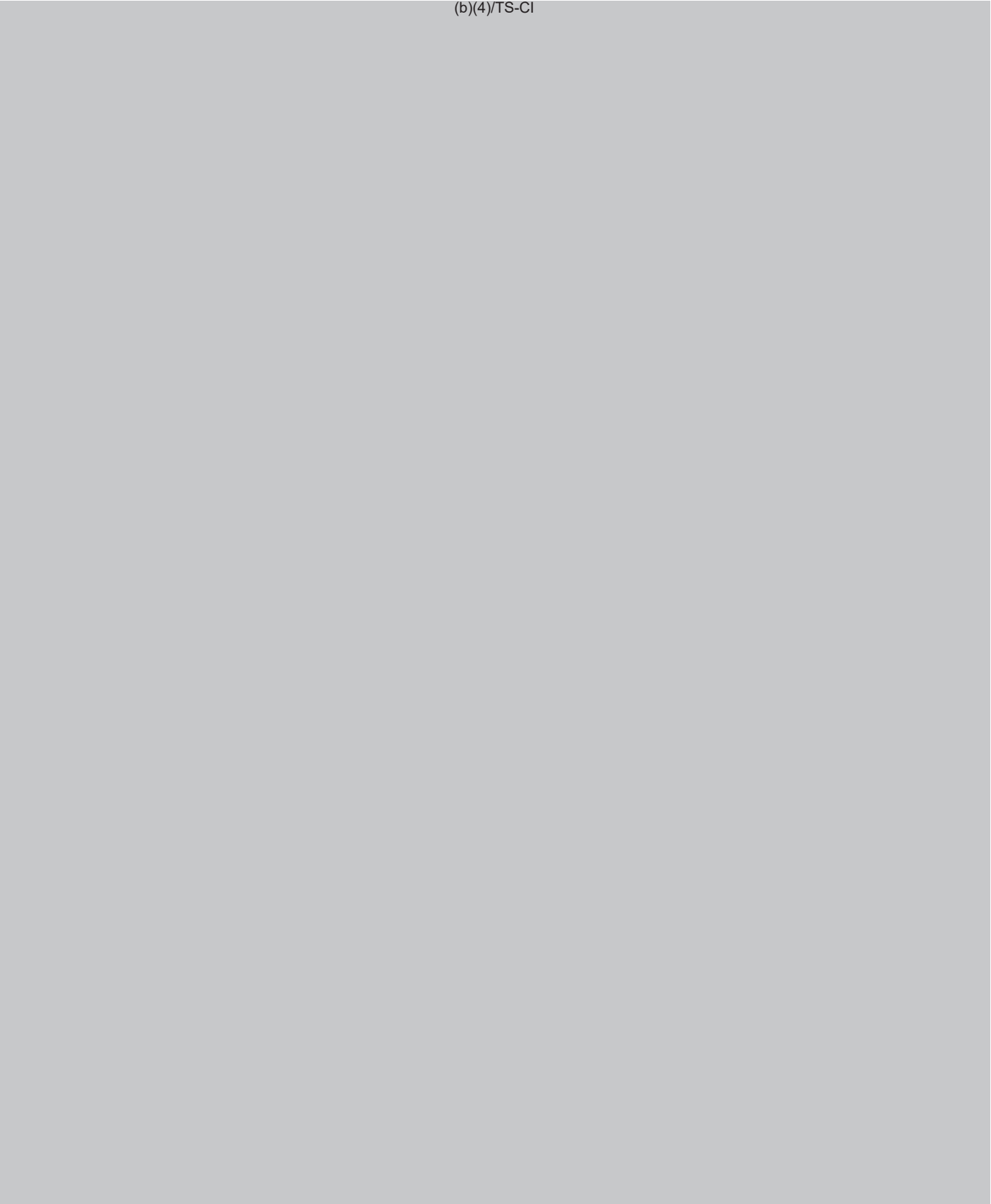
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**DEAR119**

2023 SUPP 000313

REMS Modification Comparison

1

The Mifepristone REMS Program PROPOSED MODIFICATIONS – ANNOTATED SIDE BY SIDE COMPARISON

Legend

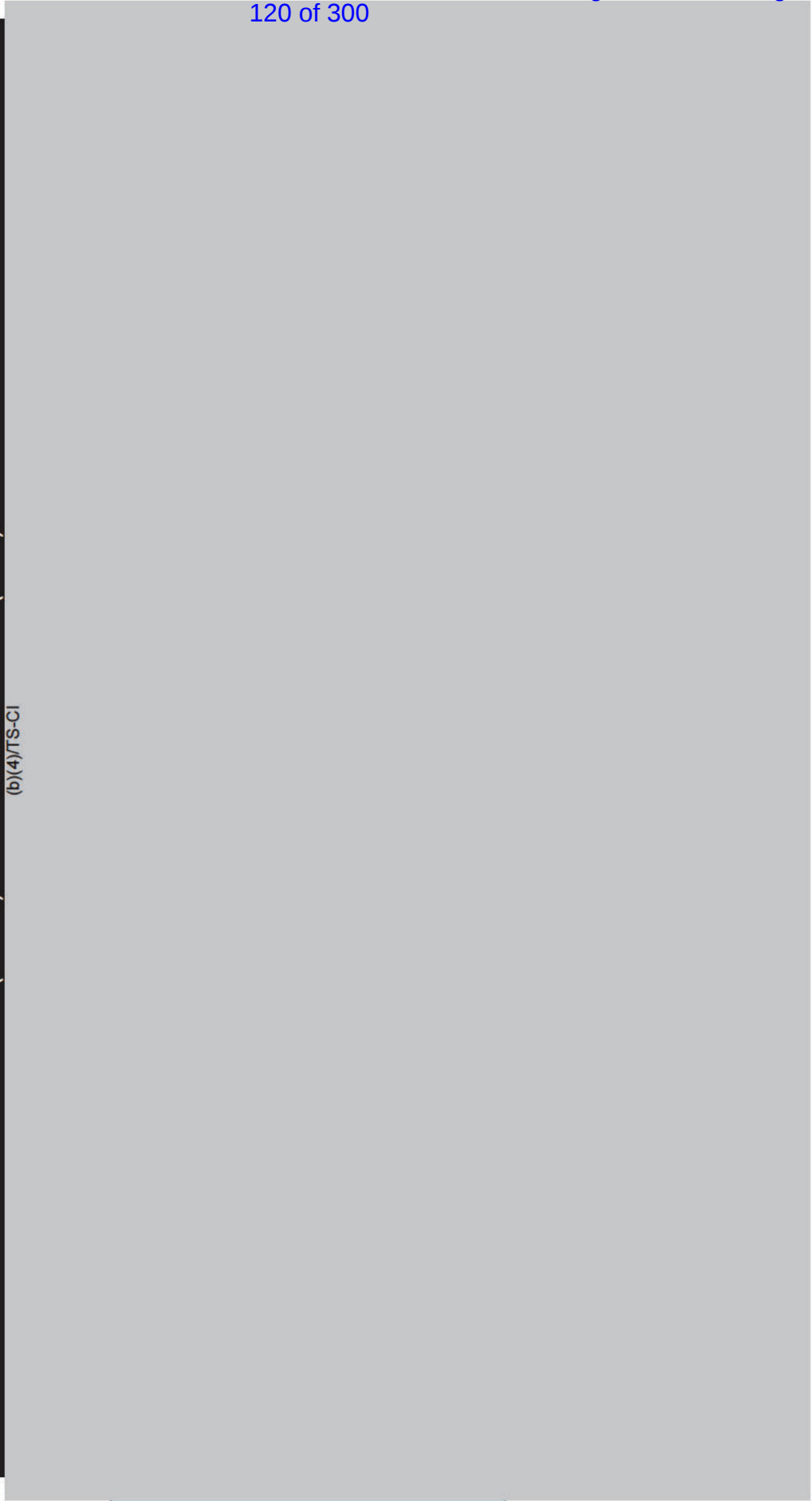
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Sponsor Specific Information

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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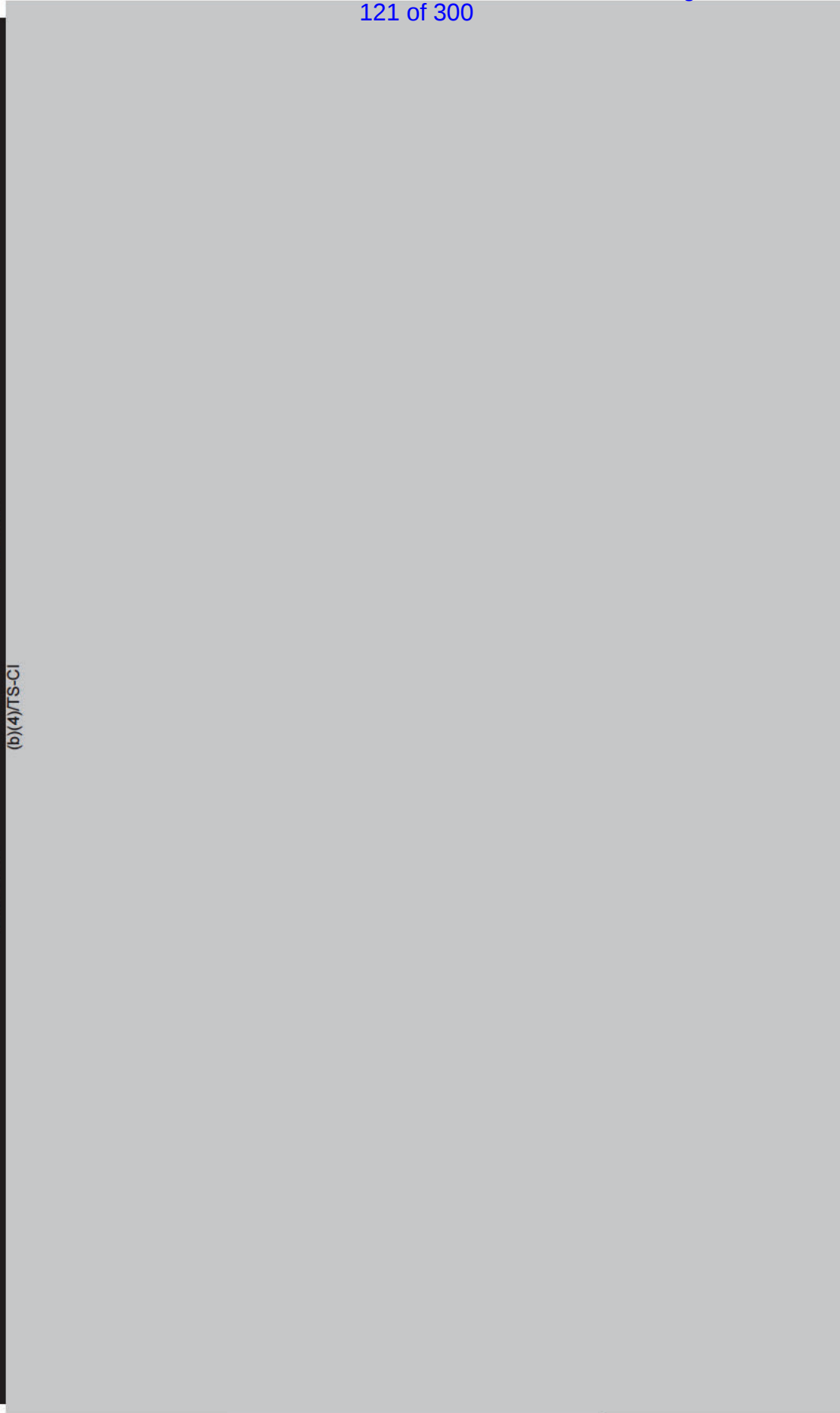
2023 SUPP 000314

REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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(b)(4)/TS-CI



JUN18 FINAL - FINAL

DEAR121

2023 SUPP 000315

REMS Modification Comparison

3

CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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(b)(4)/TS-CI



JUN18 FINAL - FINAL

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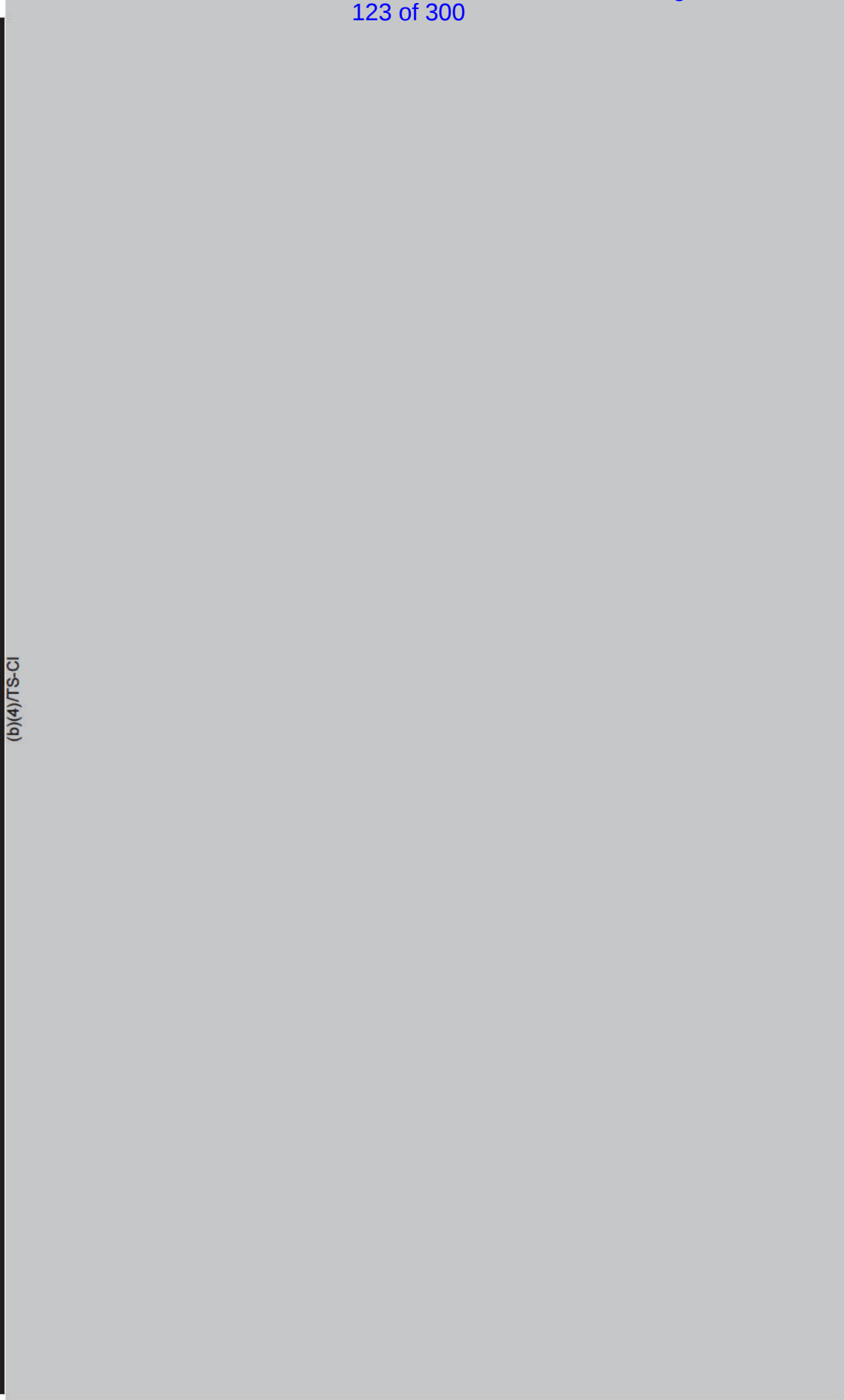
2023 SUPP 000316

REMS Modification Comparison

4

CURRENT REMS      PROPOSED REVISIONS (Redline)      PROPOSED REVISIONS (Clean)      REASON FOR MODIFICATION

(b)(4)/TS-CI



JUN18 FINAL - FINAL

DEAR123

2023 SUPP 000317

REMS Modification Comparison

5

CURRENT REMS

PROPOSED REVISIONS  
(Redline)

PROPOSED REVISIONS  
(Clean)

REASON FOR MODIFICATION

(b)(4)/TS-CI

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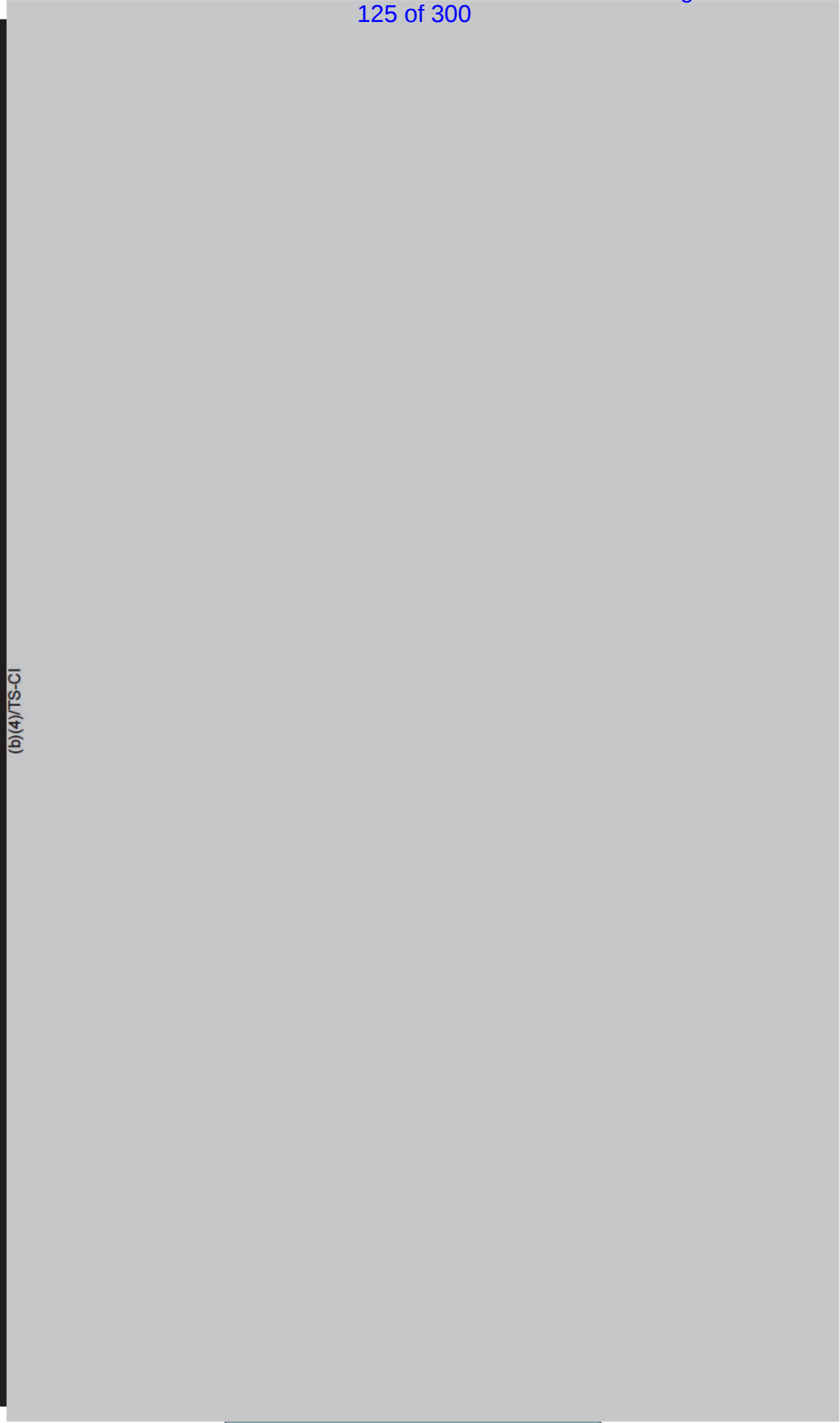
2023 SUPP 000318

REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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(b)(4)/TS-CI



JUN18 FINAL - FINAL

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REMS Modification Comparison

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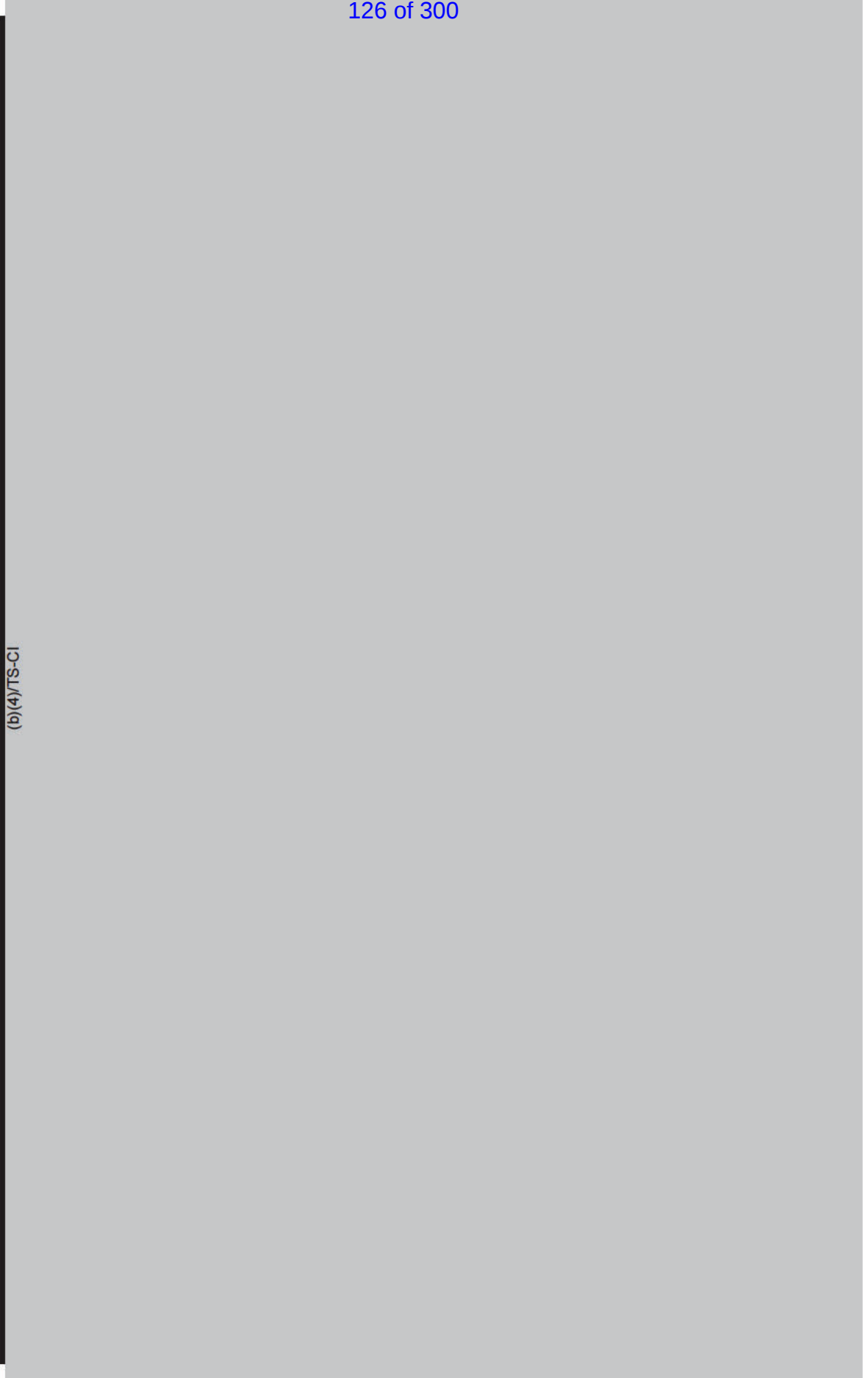
CURRENT REMS

PROPOSED REVISIONS  
(Redline)

PROPOSED REVISIONS  
(Clean)

REASON FOR MODIFICATION

(b)(4)/TS-CI



JUN18 FINAL - FINAL

DEAR126

2023 SUPP 000320

REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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(b)(4)/TS-CI



JUN18 FINAL - FINAL

DEAR127

2023 SUPP 000321

REMS Modification Comparison

9

CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
(b)(4)/TS-CI			

JUN18 FINAL - FINAL

DEAR128

2023 SUPP 000322

REMS Modification Comparison

10

CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
(b)(4)/TS-CI			

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2023 SUPP 000323

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(b)(4)/TS-CI

REMS Modification Comparison

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DEAR130

2023 SUPP 000324

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(b)(4)/TS-CI

REMS Modification Comparison

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REMS Modification Comparison

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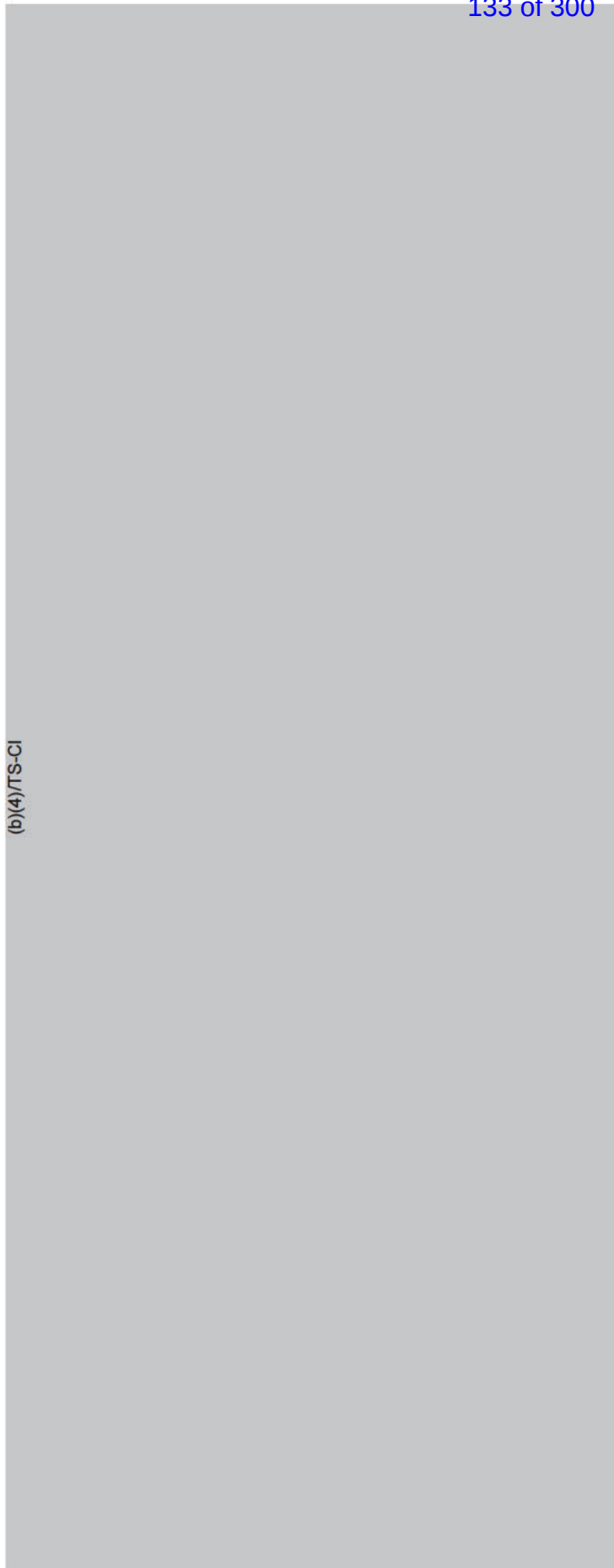
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2023 SUPP 000326

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REMS Modification Comparison

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2023 SUPP 000327

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REMS Modification Comparison

JUN18 FINAL - FINAL

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2023 SUPP 000328

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(b)(4)/TS-CI

REMS Modification Comparison

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2023 SUPP 000329

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REMS Modification Comparison

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REMS Modification Comparison

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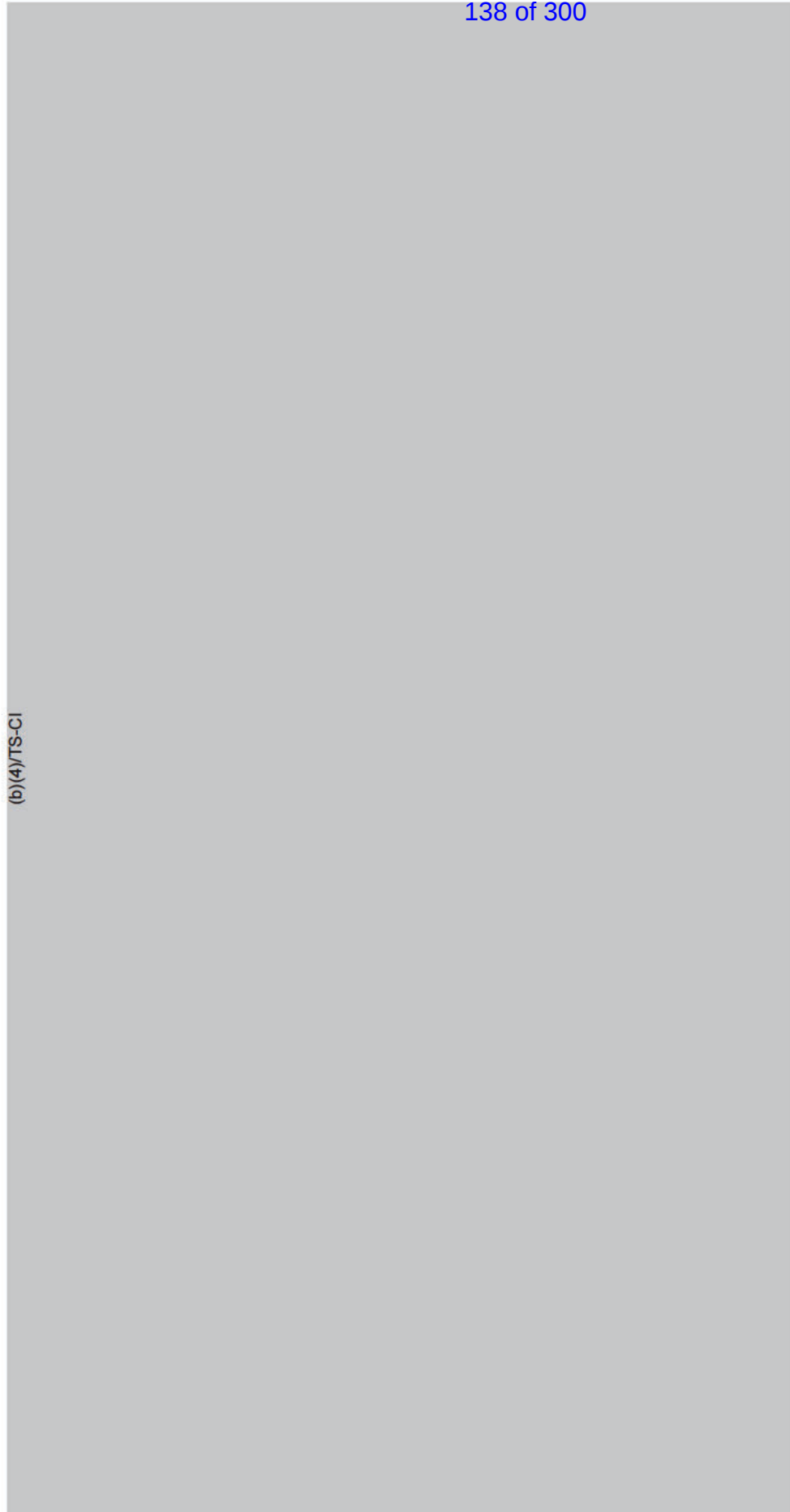
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REMS Modification Comparison

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2023 SUPP 000332

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REMS Modification Comparison

JUN18 FINAL - FINAL

DEAR139

2023 SUPP 000333

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REMS Modification Comparison

JUN18 FINAL - FINAL

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2023 SUPP 000334

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(b)(4)/TS-CI

REMS Modification Comparison

JUN18 FINAL - FINAL

DEAR141

2023 SUPP 000335

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REMS Modification Comparison

(b)(4)/TS-CI

JUN18 FINAL - FINAL

DEAR142

2023 SUPP 000336

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(b)(4)/TS-CI

REMS Modification Comparison

JUN18 FINAL - FINAL

DEAR143

2023 SUPP 000337

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REMS Modification Comparison

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2023 SUPP 000338

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REMS Modification Comparison

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2023 SUPP 000339

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## 1.16.2 Summary of the Proposed REMS Modifications

### 1. Introduction

On December 16, 2021, the Agency directed Danco Laboratories, LLC (“Danco”) and GenBioPro, Inc. (“GenBioPro”) (collectively, the “Sponsors”) in a [REMS Modification Notification dated December 16, 2021](#) to modify the Mifepristone SSS REMS (the “REMS”) as follows:

**Elements to Assure Safe Use:** We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will reduce the burden on the healthcare delivery system of complying with the REMS.

**Elements to Assure Safe Use:** Pursuant to §505-1(f)(1) [of the Food, Drug, and Cosmetic Act], we have also determined that an additional element to assure safe use is necessary to mitigate the risk of serious complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers who prescribe the drugs have particular experience or training, or are specially certified[.]
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified[.]
- The drug is dispensed to patients with evidence or other documentation of safe use conditions.

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

On March 11, 2022, the Sponsors submitted a Type A Meeting Request including questions regarding the REMS Modification to which the Agency provided [Written Responses on April 8, 2022](#).

GenBioPro and Danco have worked collaboratively to modify the REMS for mifepristone as directed by FDA.

This document summarizes and provides further explanation for the proposed Modifications to the mifepristone REMS and serves as the adequate rationale for the REMS Modifications to the extent required by § 505-1(g)(4)(A) of the Food, Drug, and Cosmetic Act (FDCA). Additionally, a detailed side-by-side annotated comparison of the proposed modified REMS versus the approved REMS is provided in [Section 1.16.2.2](#).

## 2. Background

Based on FDA's review of published literature, safety information collected during the ongoing COVID-19 public health emergency, FDA Adverse Event Reporting Systems (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, and parties in ongoing litigation, FDA determined that the in-person dispensing requirement is no longer necessary to ensure the benefit of the drug outweigh the risk and that modification of the REMS to add pharmacy certification is necessary to allow dispensing by pharmacies.

The proposed Modifications to the REMS and REMS materials were developed to allow for mifepristone to be prescribed by certified prescribers [REDACTED] (b)(4)/TS-CI [REDACTED], without imposing in-person assessment, counseling, consenting, prescribing or follow-up requirements. In addition, the proposed Modifications provide for mifepristone to be dispensed by mail/courier (as well as in person) by or under the supervision of certified prescribers or by certified pharmacies, while meeting the statutory requirement under §505-1(f)(2)(B) of the FDCA to minimize the burden on the health care system and not be unduly burdensome on patient access to the drug (especially to patients who have difficulty accessing health care, such as patients in rural or medically underserved areas or who have other limitations).

In developing the modified REMS, the Sponsors considered both the FDA's responses (in its [Written Response](#)) to the Sponsors' questions and their extensive experience with the use and distribution of mifepristone, including the experience gained over the last two years with the provision of mifepristone through telemedicine and mail delivery by healthcare providers and mail-order pharmacies. They have also consulted with a broad range of stakeholders, including current and potential prescribers, mail and retail pharmacies, distributors, and other experts to develop REMS Modifications that would best meet the FDA directive to improve access and maintain safe use without imposing undue burdens on patients and stakeholders.

The Sponsors' proposed REMS includes several interrelated elements to implement the REMS to meet the Agency's objectives and mandate under §505-1(f)(2)(B) while avoiding the unintended effect of limiting access, increasing burdens, and introducing risks to healthcare provider and patient confidentiality. In that regard, the proposed modified REMS is intended to meet the applicable legal standards and reflect FDA's considered view of what conditions are necessary for the safe use of mifepristone for the intended use, such that additional restrictions would be

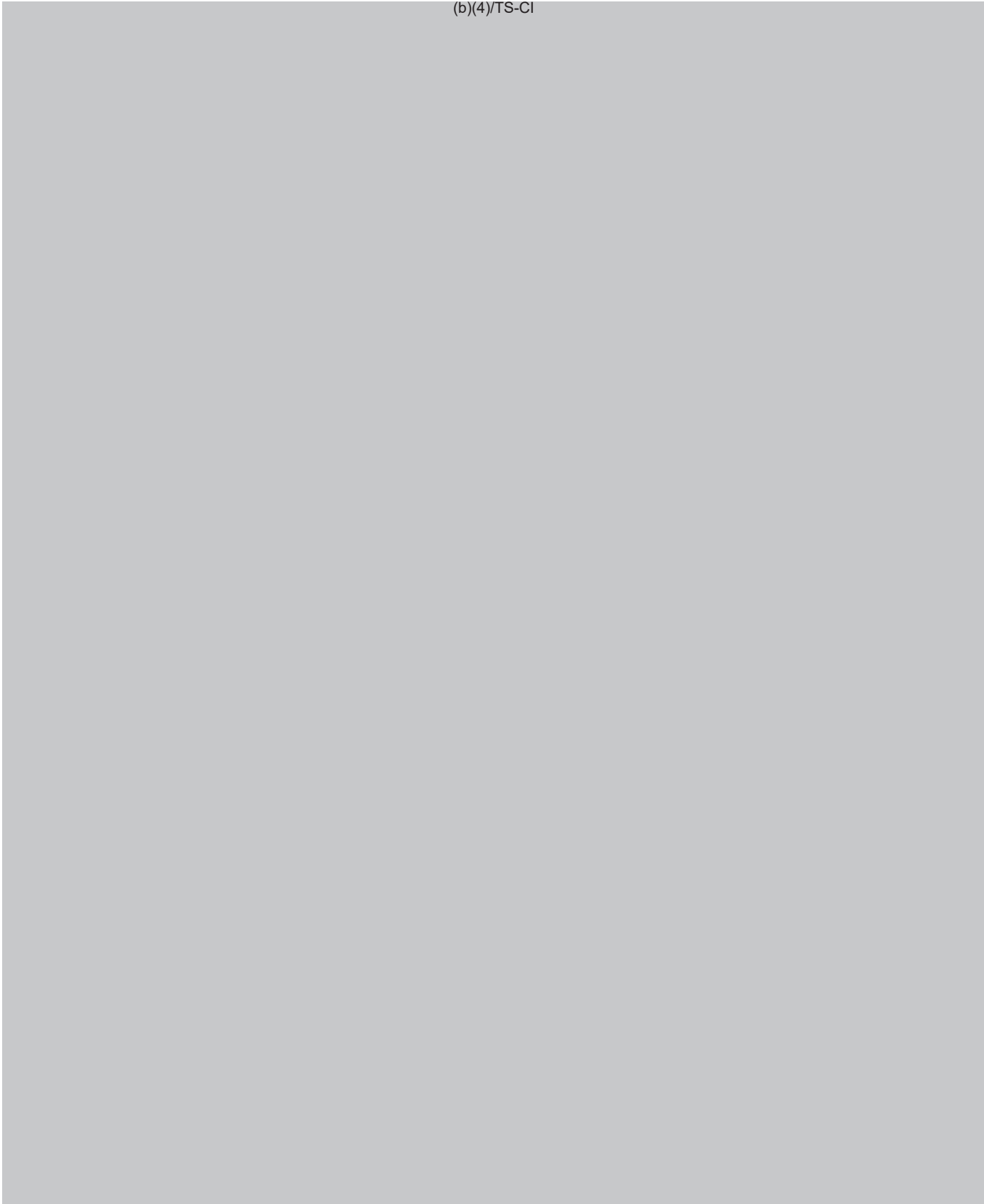
inconsistent with the conditions of use (including its labeling, distribution, prescribing, dispensing and use) established by the Agency under its unique and exclusive statutory authority, mandates and recognized expertise. We ask FDA to carefully evaluate our proposed Modifications, as a suitable approach to assure that patient access to mifepristone under such restrictions as necessary to safe use.

The proposed Modified REMS includes the following:

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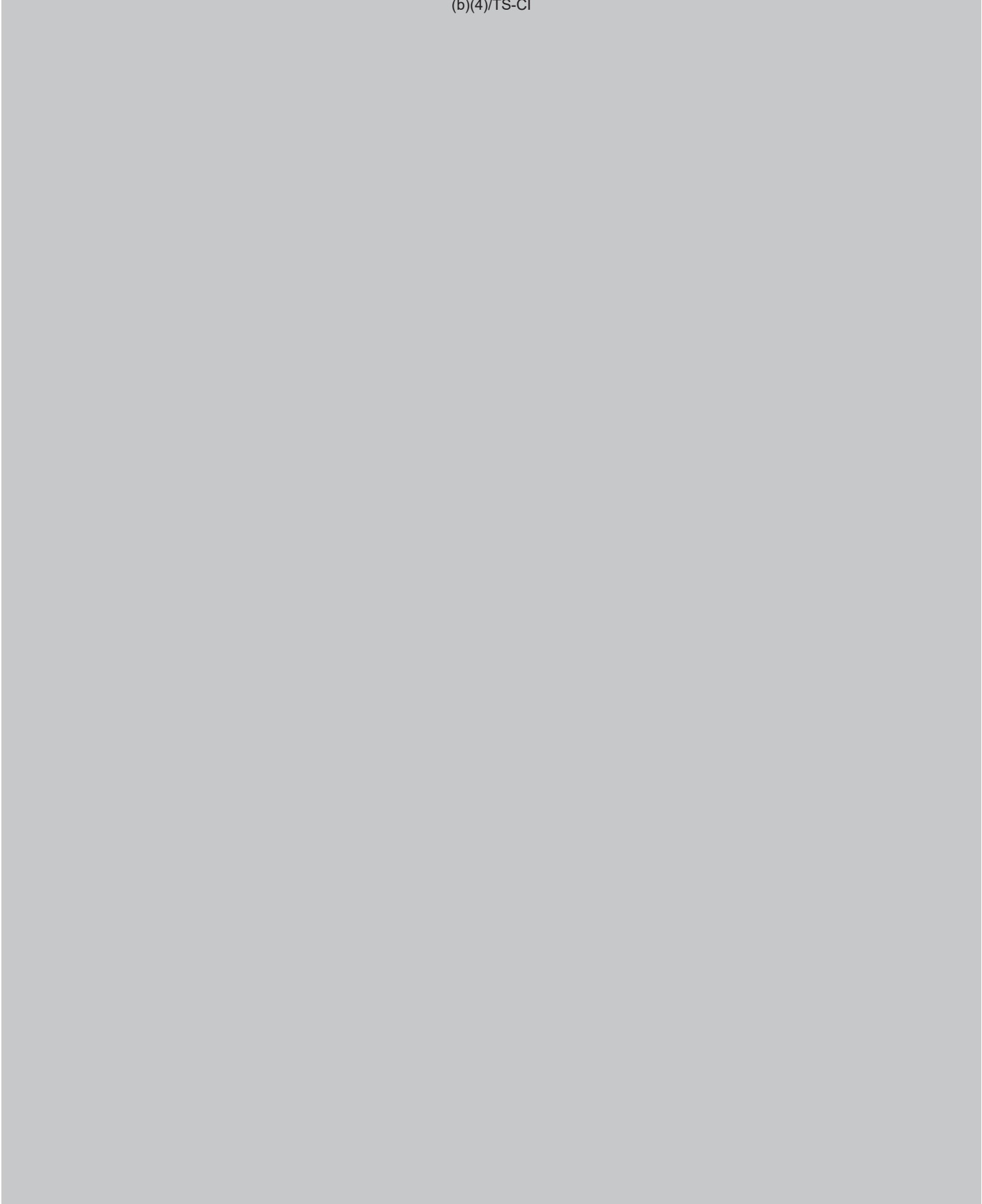


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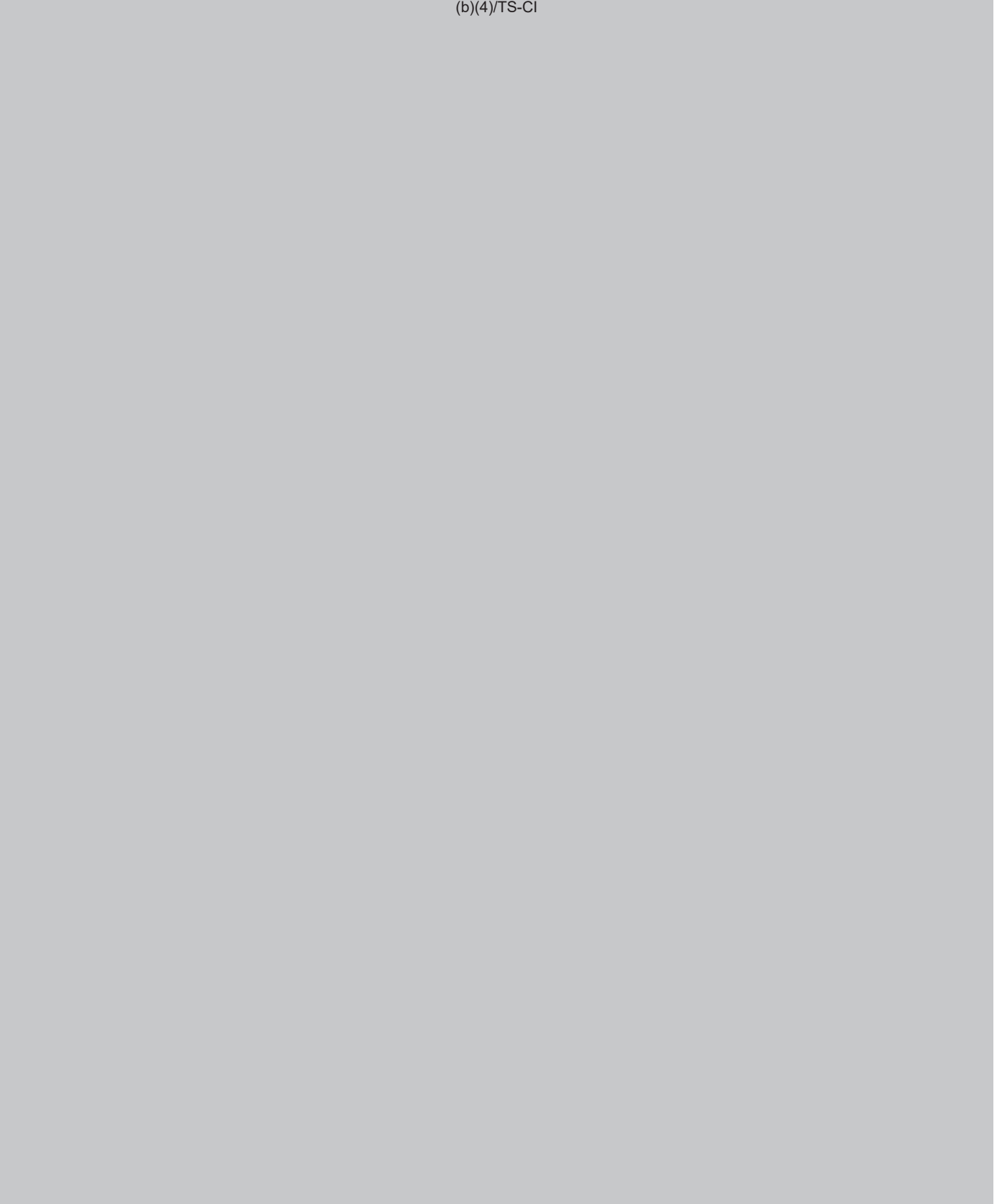
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GenBioPro, Inc.  
P.O. Box 32011  
Las Vegas, NV 89103

**NEW SUPPLEMENT FOR ANDA 091178/S-004  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

June 22, 2022

(b)(6)/PPI

Center for Drug Evaluation and Research  
Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993-0002

**Re: ANDA 091178, Sequence No. 0087  
Mifepristone tablets, 200 mg  
PRIOR APPROVAL SUPPLEMENT S-004  
PROPOSED MAJOR SSS REMS MODIFICATION  
PROPOSED CHANGES TO LABELING AND MEDICATION GUIDE**

Dear (b)(6)/PPI

This prior approval ANDA supplement 004 is being submitted by GenBioPro, Inc. in response to FDA's [REMS Modification Notification dated December 16, 2021](#). This supplement addresses FDA's determination that the approved Mifepristone Single Shared System Risk Evaluation and Mitigation Strategy ("SSS REMS") must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

Danco and GenBioPro have worked collaboratively to modify the SSS REMS to include the necessary elements to assure safe use of mifepristone. Danco will be submitting identical documents to their NDA 020687, adjusted for company name and other proprietary information.

The proposed major modifications to the SSS REMS were developed based on the recommendations provided by FDA in the REMS Modification Notification as well as feedback received in the Type A Meeting Written Response communication dated [April 08, 2022](#) ("Written Response"). Additionally, the Full Prescribing Information, and the Medication Guide have been revised to align with the modifications to the SSS REMS. All revised documents include gender neutral adjustments where indicated.

\* This document constitutes trade secret and confidential commercial information exempt from public disclosure under **21 C.F.R. 20.61**. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Applicant requests immediate notification and an opportunity for consultation in accordance with **21 C.F.R. 20.45**.

**DEAR157**

**2023 SUPP 000351**

The below list of documents are included in this submission.

Documents Provided in this Submission	eCTD Location
Summary of Changes <a href="#">Summary of Modifications to Mifepristone SSS REMS</a>	<a href="#">1.16.2.2</a>
Mifepristone SSS REMS Proposed Modification  <a href="#">Mifepristone SSS REMS Modification – TRACK CHANGES MS Word version</a>  <a href="#">Mifepristone SSS REMS Modification – CLEAN MS Word version</a>  <a href="#">Side-by-Side Comparison of the SSS REMS Modification and REMS Materials with the Current SSS REMS and REMS Materials</a>	<a href="#">1.16.2.2</a>  <a href="#">1.16.2.2</a>  <a href="#">1.16.2.2</a>
Revised Patient Agreement  <a href="#">Revised Patient Agreement –TRACK CHANGES MS Word version</a>  <a href="#">Revised Patient Agreement – CLEAN MS Word version</a>	<a href="#">1.16.2.2</a>  <a href="#">1.16.2.2</a>
Revised Prescriber Agreement  <a href="#">Revised Prescriber Agreement – (GenBioPro) TRACK CHANGES MS Word version</a>  <a href="#">Revised Prescriber Agreement – (GenBioPro) CLEAN MS Word version</a>	<a href="#">1.16.2.2</a>  <a href="#">1.16.2.2</a>
New Proposed Pharmacy Agreement  <a href="#">New Proposed Pharmacy Agreement (GenBioPro) – MS Word</a>	<a href="#">1.16.2.2</a>

\* This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Applicant requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45.

Documents Provided in this Submission	eCTD Location
Revised REMS Supporting Document  <a href="#">REMS Supporting Document – TRACK CHANGES MS Word version</a>  <a href="#">REMS Supporting Document – CLEAN MS Word version</a>	  <a href="#">1.16.2.2</a>  <a href="#">1.16.2.2</a>
Revised Full Prescribing Information and Medication Guide  <a href="#">Revised Full Prescribing Information and Medication Guide – (GenBioPro) Redline Annotated MS Word version</a>  <a href="#">Revised Full Prescribing Information and Medication Guide – (GenBioPro) Clean MS Word version</a>	  <a href="#">1.14.1.2</a>  <a href="#">1.14.1.2</a>

If there are any questions regarding this submission, please do not hesitate to contact me directly.

Sincerely,

(b)(4)/TS-CI; (b)(6)/PPI

GenBioPro, Inc.

(b)(4)/TS-CI; (b)(6)/PPI

(mobile)

(b)(4)/TS-CI; (b)(6)/PPI

\* This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Applicant requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45.

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2023 SUPP 000353

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NDA 020687

**MEETING REQUEST-  
WRITTEN RESPONSES**

Danco Laboratories, LLC

(b)(4)/TS-CI; (b)(6)/PPI

P.O. Box 4816  
New York, NY 10185

Dear (b)(4)/TS-CI; (b)(6)/PPI

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mifeprex (mifepristone) Tablets.

We also refer to your submission dated March 11, 2022, containing a meeting request. The purpose of the requested meeting was to discuss the proposed modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg, the REMS materials, and other supporting documents to facilitate a submission by April 15, 2022.

Further reference is made to our Meeting Granted letter dated March 16, 2022, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your March 11, 2022, background package.

If you have any questions, (b)(6)/PPI

Sincerely,

*{See appended electronic signature page}*

(b)(6)/PPI

Center for Drug Evaluation and Research

Enclosure:

- Written Responses

NDA 020687

Page 2

## WRITTEN RESPONSES

**Meeting Type:** Type A  
**Meeting Category:** Post-Action Meeting, REMS

**Application Number:** 020687

**Product Name:** Mifeprex (mifepristone) Tablets

**Indication:** Mifepristone, in a regimen with misoprostol, is indicated for the medical termination of intrauterine pregnancy through 70 days gestation

**Applicant Name:** Danco Laboratories, LLC

## BACKGROUND

On December 16, 2021, FDA issued a letter to notify the applicants of mifepristone for medical termination of early pregnancy that the single, shared system REMS must be modified as follows:

**Elements to Assure Safe Use:** FDA determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will also minimize the burden on the healthcare delivery system of complying with the REMS.

**Elements to Assure Safe Use:** Pursuant to 505-1(f)(1), FDA also determined that an additional element to assure safe use is necessary to mitigate the risk of serious complications associated with mifepristone listed in the labeling of the drug. Modification of the REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

NDA 020687

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## QUESTIONS AND RESPONSES

### Question 1: For pharmacies that will dispense mifepristone:

**Question 1 a):** Will the Agency accept a certification process and requirements that are the same for pharmacies dispensing by mail or local courier and pharmacies dispensing in-person to the patient?

**FDA Response:** *You may propose the same certification for different pharmacy dispensing models. However, we may need additional information on your proposal depending on your dispensing model. A review of your proposed REMS modifications will be necessary to determine if your overall proposal for pharmacy certification assures the safe use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation.*

**Question 1 b):** Is certification of an authorized representative of the pharmacy on behalf of all of its multiple locations and personnel acceptable to the Agency for the revised mifepristone REMS?

**FDA Response:** *Yes, a pharmacy can designate an authorized representative to carry out the certification process regardless of whether that pharmacy has one location or multiple locations. Note that the authorized representative is responsible for and must agree to oversee implementation of and compliance with the Mifepristone REMS Program. In addition, as part of your proposed implementation system, you must have a process to ensure that the pharmacies distributing mifepristone comply with the Mifepristone REMS Program requirements for certified pharmacies. In your submission, describe how you would implement and monitor compliance by certified pharmacies with the Mifepristone REMS Program requirements.*

**Question 1 c):** Would FDA consider approving Pharmacy Certification with the following requirements and advise on other elements that also need to be addressed?

Requirements: The pharmacy, through its authorized representative, certifies that it will implement necessary actions to ensure the following:

- (i) Dispense mifepristone only under prescriptions issued by (b)(4)/TS-CI a certified prescriber (see below for contemplated verification and questions on certified prescribers);
- (ii) No transfer of mifepristone other than to a patient per above, a certified prescriber, another certified pharmacy, or for returns or destruction;
- (iii) Communicate any reported deaths of mifepristone users to the prescriber;

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NDA 020687

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- (iv) The Medication Guide is available to patients;
- (v) Maintain records of the above and accept audits; and
- (vi) Protect the confidentiality and privacy of providers and patients.

***FDA Response:*** *Specifics on pharmacy requirements will be a matter of FDA review. At this time, we have insufficient information regarding permitting mifepristone to be transferred from one certified pharmacy to another certified pharmacy or from a certified pharmacy to a certified prescriber. In your submission, provide your rationale and examples of when and how such a transfer would occur. We encourage you to review the Format and Content of a REMS Document Guidance for Industry which can be found at [Format and Content of a REMS Document Guidance for Industry | FDA](#).*

*In general, we agree with your proposal for (iii), (iv), (v), and (vi) but specific details will be a review issue. See our response to question 1 d) for (i).*

**Question 1 d):** As the Agency understands, providing medical abortion with mifepristone may expose prescribers to extreme risks to their safety that are different from any other drug product. The ever-present risk of anti-abortion violence creates material security and confidentiality risks for mifepristone prescribers, distributors, pharmacies, and patients. Accordingly, care must be taken to ensure that any modification to the Mifepristone REMS Program does not create a risk of unauthorized disclosure of identifying information about any of these stakeholders. (b)(4)/TS-CI

. Any apparent or potential risk would cause many prescribers—including existing prescribers—to refrain from becoming or remaining mifepristone prescribers.

Nonetheless, the Sponsors assume that, if mifepristone is to be dispensed by pharmacies, the REMS must include a process by which a pharmacy first confirms that the prescriber is specially certified. Currently the prescriber verification process is handled by the distributors for each product, each of which receives a Prescriber Agreement and distributes product only on the basis of a valid order from a certified prescriber. The number of distributors and prescribers is quite small; however, the nature and size of a prescriber certification system for dispensing pharmacies present potential disclosure risk of an entirely different magnitude. (b)(4)/TS-CI

. In short, the critical elements of an effective system must reconcile prescriber security and confidentiality, while providing reasonable

NDA 020687

Page 5

assurance that pharmacies dispense only in response to a valid prescription from a specially certified prescriber.

With that in mind, would the Agency consider or comment on a verification system that includes the following elements:

(i)

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(ii) The pharmacy must keep prescription records.

***FDA Response:*** *The verification process for safe use conditions by the pharmacy is a matter of FDA review.*

(b)(4)/TS-CI

*In your submission, specify how you would implement and monitor compliance with this requirement.*

**Question 2:** In accordance with the Mifepristone REMS Program, medical assessment, counseling, and follow-up are carried out by healthcare professionals and qualified persons acting under the supervision of the certified prescriber responsible for assuring compliance with required procedures. To eliminate confusion for healthcare providers, this should be expressly recognized as an acceptable approach for mifepristone prescribing under the REMS.

Accordingly, would FDA consider or accept an explicit clarification to the REMS that prescriber certification establishes the certification of the prescriber and the healthcare providers who are working by or under their supervision?

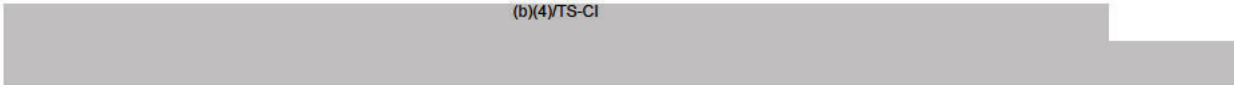




***FDA Response:*** *Yes. The Prescriber Agreement Form could be revised for the certified prescriber to stipulate that assessment, counseling, prescribing, and follow-up may be conducted by the certified prescriber and health care providers who are working under the supervision of the certified prescriber. Propose specific edits to the Prescriber Agreement Form to address this issue.*

**Question 3:**

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NDA 020687

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**FDA Response:**(b)(4)/TS-CI  
**Question 4:**(b)(4)/TS-CI  
  
**FDA Response:**(b)(4)/TS-CI  


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/s/  
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(b)(6)/PPI

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**FDA U.S. FOOD & DRUG**  
ADMINISTRATION

ANDA 091178

## REMS MODIFICATION NOTIFICATION

GenBioPro Inc

(b)(4)/TS-CI; (b)(6)/PPI

US Agent for GenBioPro, Inc.

Dear (b)(4)/TS-CI; (b)(6)/PPI

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for mifepristone tablets.

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

The Shared System (SS) REMS for mifepristone consists of elements to assure safe use, and an implementation system.

In accordance with section 505-1(g)(4)(B) of the FD&C Act, we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

**Elements to Assure Safe Use:** We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will reduce the burden on the healthcare delivery system of complying with the REMS.

**Elements to Assure Safe Use:** Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of

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10903 New Hampshire Avenue  
Silver Spring, MD 20903  
[www.fda.gov](http://www.fda.gov)

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2023 SUPP 000362

serious complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers who prescribe the drugs have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the ETASU (as outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your ANDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B) of the FD&C Act, you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A) of the FD&C Act.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**NEW SUPPLEMENT FOR AND A 091178/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

**AND A 091178/S-000  
PROPOSED REMS MODIFICATION-AMENDMENT**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

**SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email [REMS\\_Website@fda.hhs.gov](mailto:REMS_Website@fda.hhs.gov).

If you have any questions, call

(b)(6)/PPI

Sincerely,

*{See appended electronic signature page}*

(b)(6)/PPI

Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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**FULL PRESCRIBING INFORMATION**


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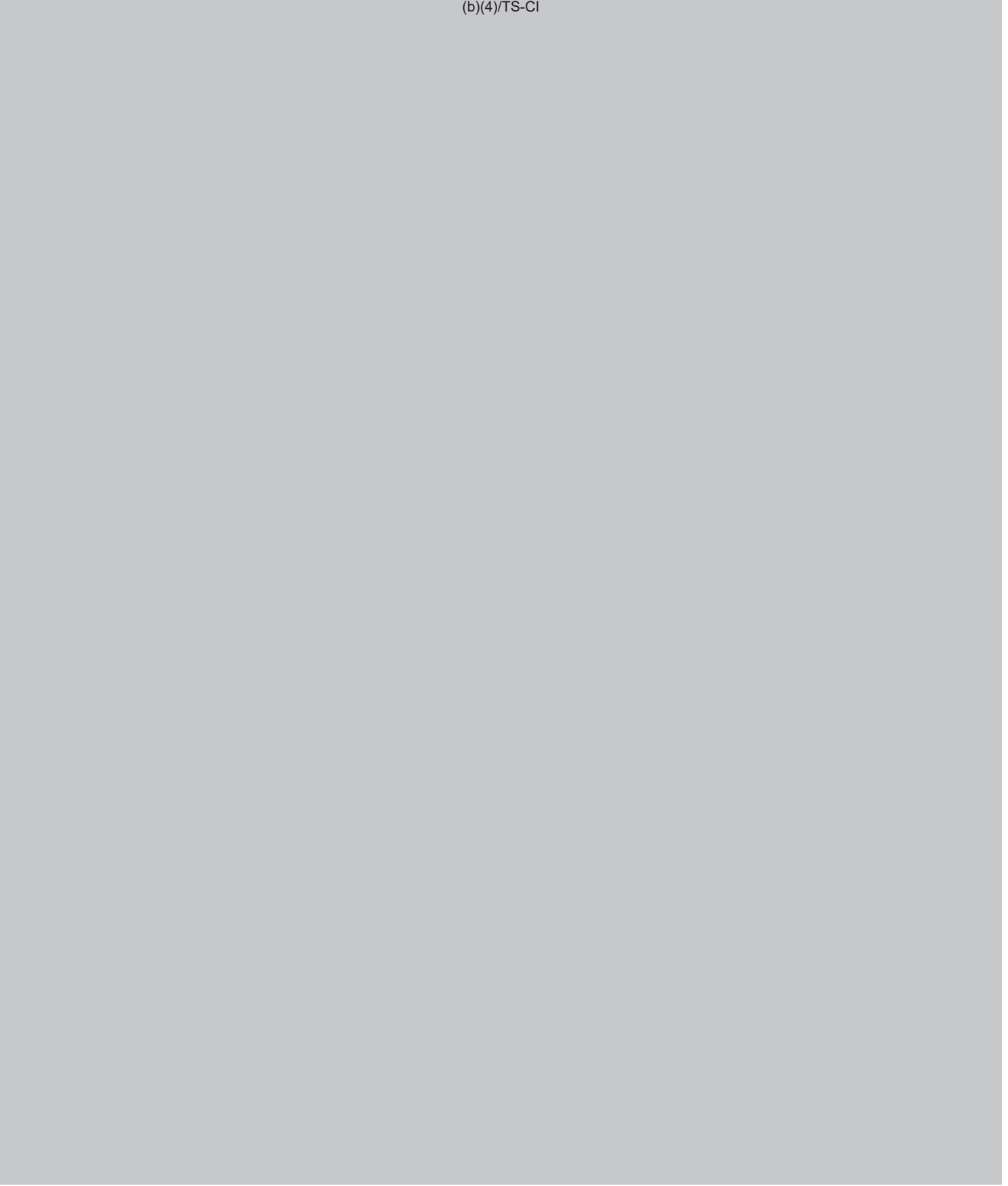
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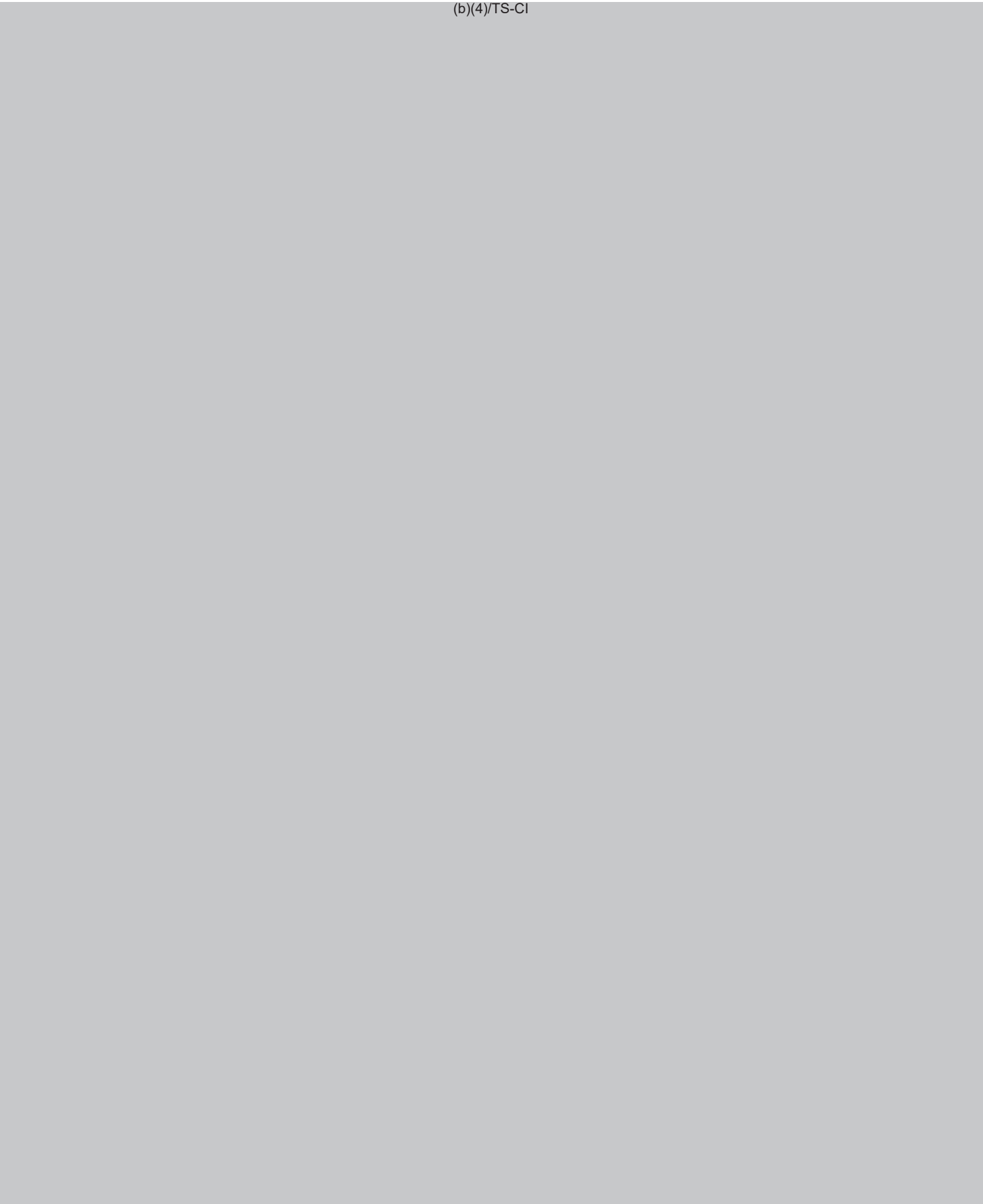
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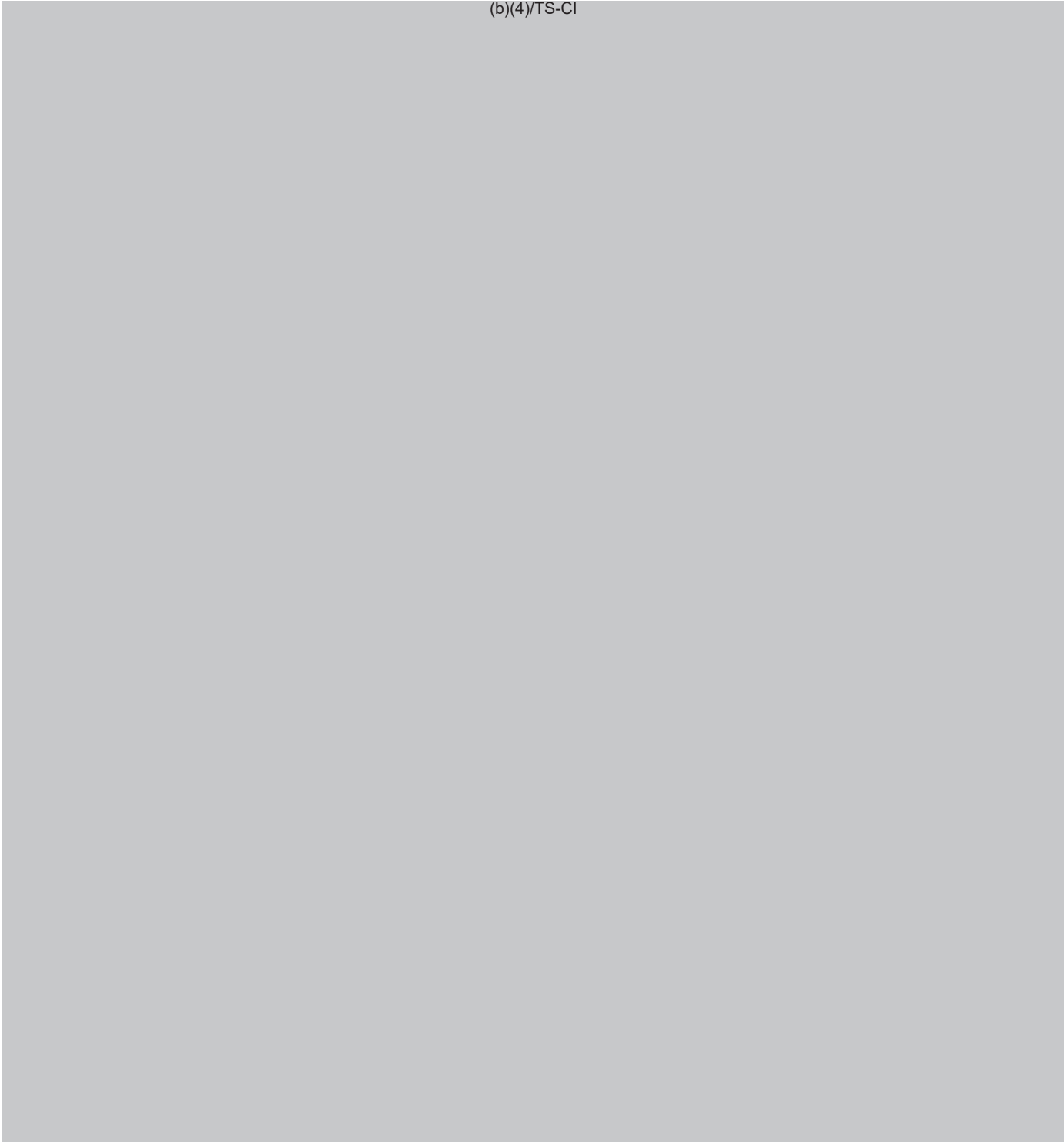


**MEDICATION GUIDE**

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Mifepristone Tablets, 200 mg

Progestin Antagonist

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

**SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200MG**

(b)(4)/TS-CI



**DEAR192**

2023 SUPP 000386

**DEAR193**

2023 SUPP 000387

(b)(4)/TS-CI



**DEAR194**

2023 SUPP 000388

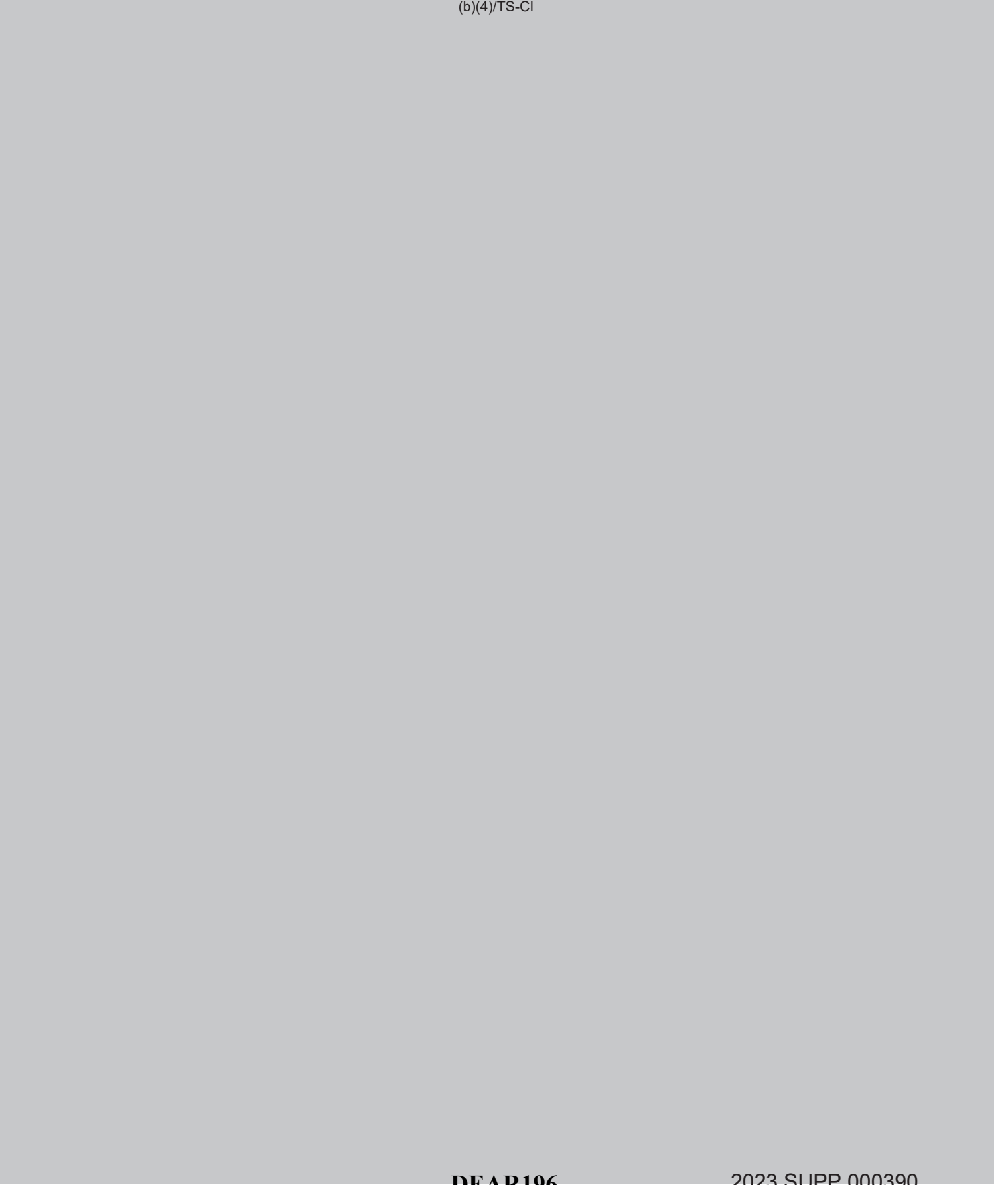
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PHARMACY AGREEMENT FORM

Mifepristone Tablets, 200 mg

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(b)(4)/TS-CI



(b)(4) TS-CI

(b)(4) TS-C

**Mifepristone Tablets, 200 mg<sup>1</sup>****SINGLE SHARED SYSTEM RISK EVALUATION AND MITIGATION STRATEGY  
(REMS) SUPPORTING DOCUMENT**

(b)(4)/TS-CI

<sup>1</sup> This document constitutes trade secret and confidential information exempt from public disclosure under 21 C.F.R. § 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, the Sponsors request immediate notification and an opportunity for consultation in accordance with 21 C.F.R. § 20.45.

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REMS Modification Comparison

1

The Mifepristone REMS Program PROPOSED MODIFICATIONS – ANNOTATED SIDE BY SIDE COMPARISON

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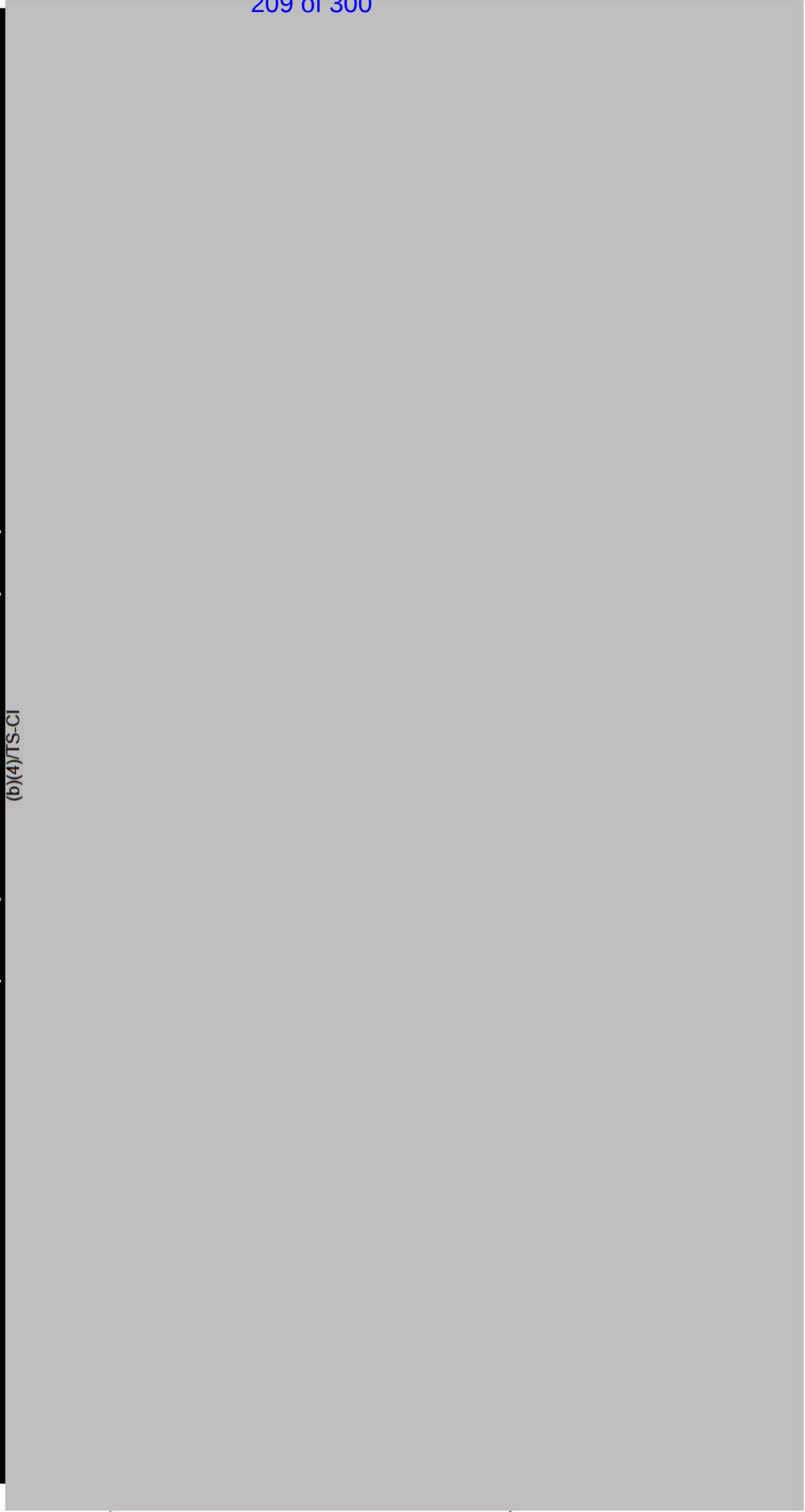
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Sponsor Specific Information

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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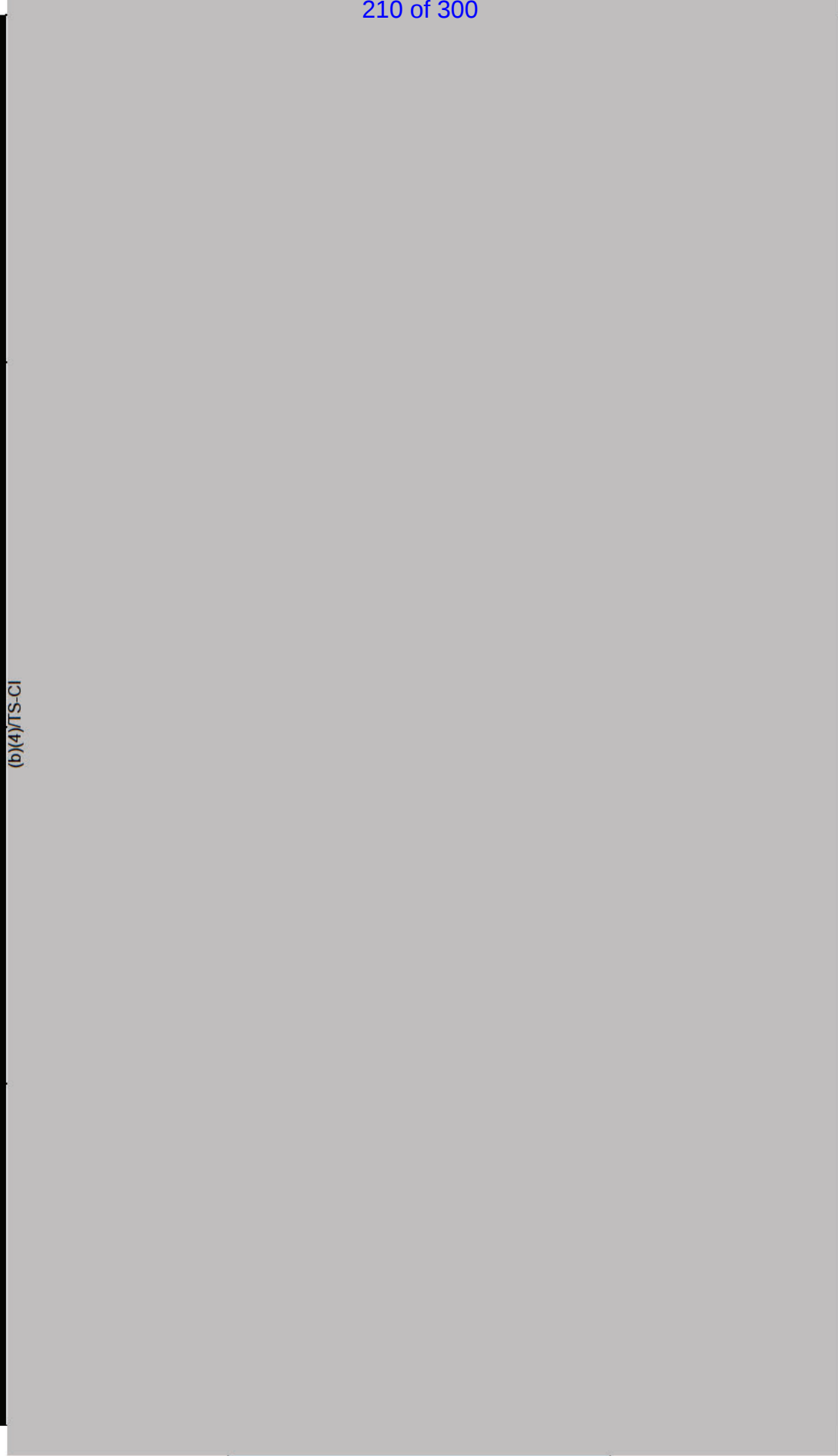
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REMS Modification Comparison

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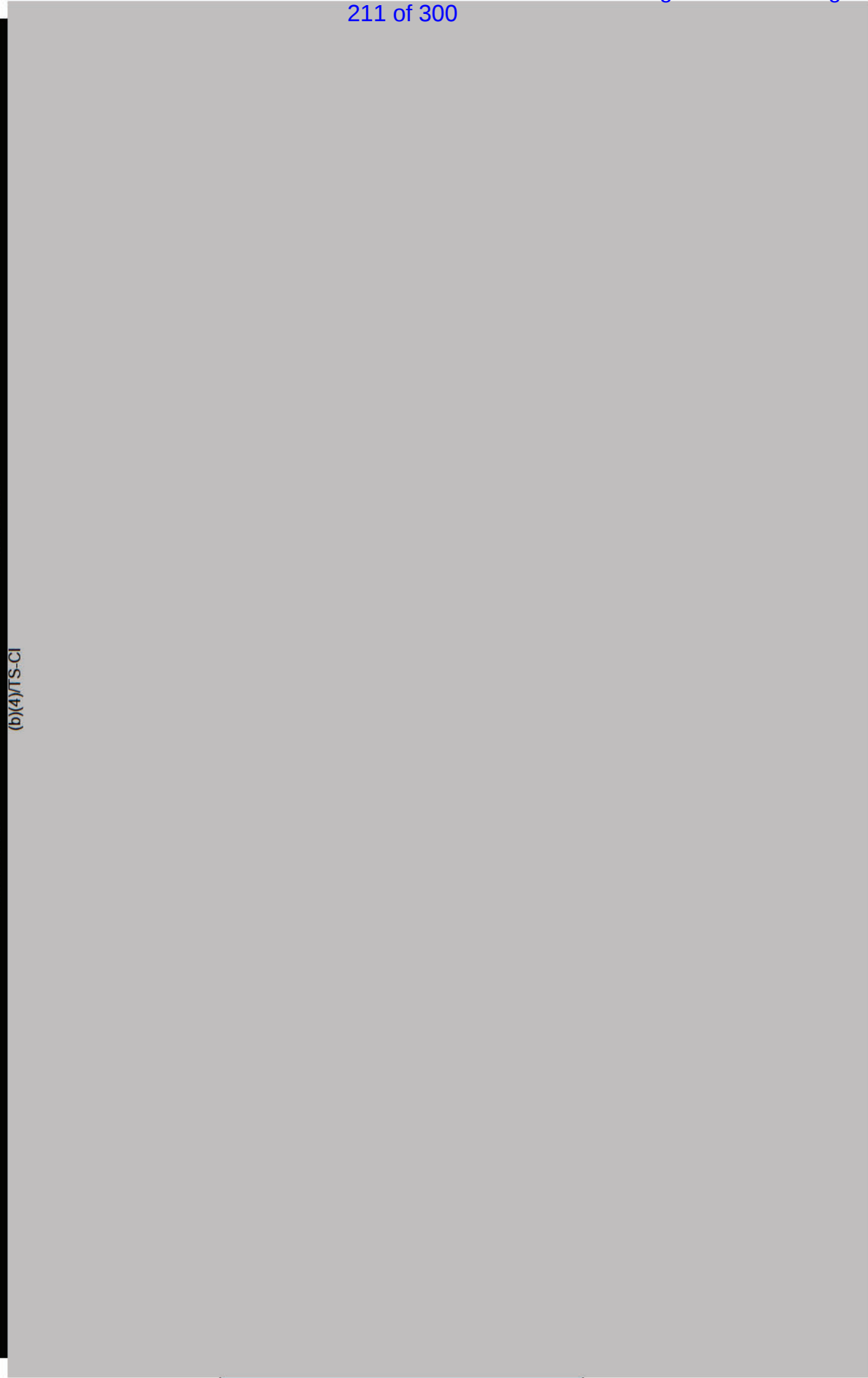
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REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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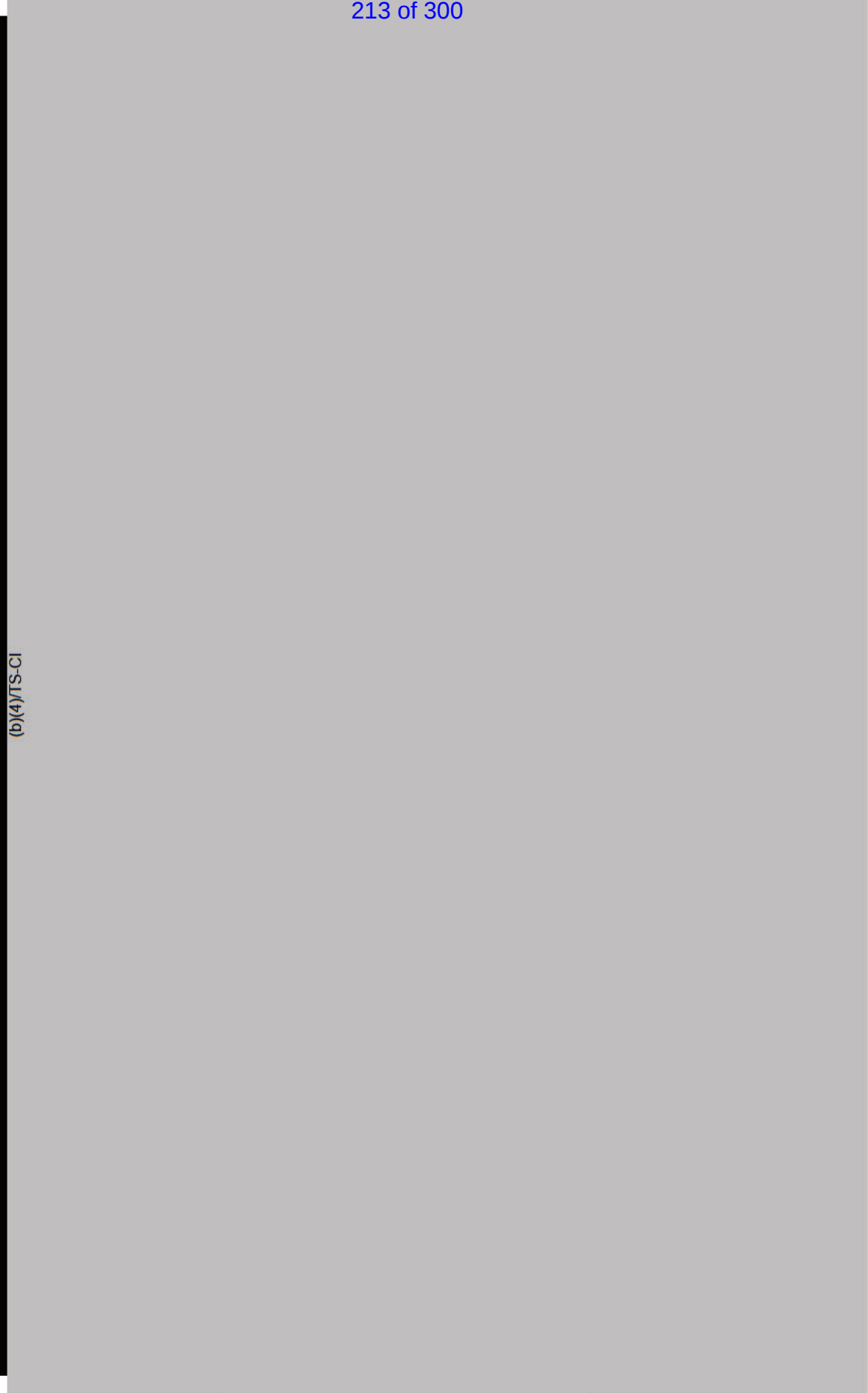
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REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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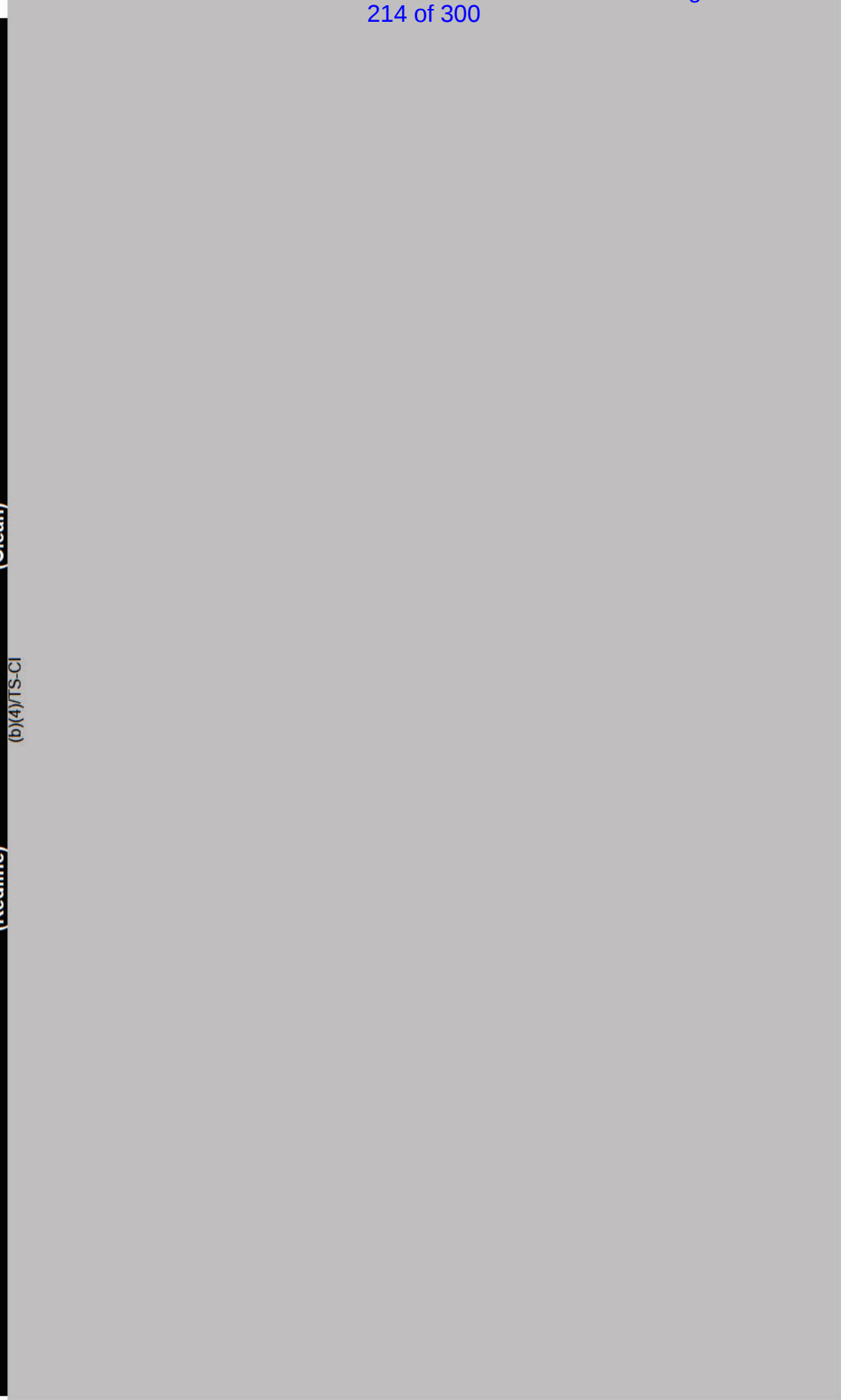
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REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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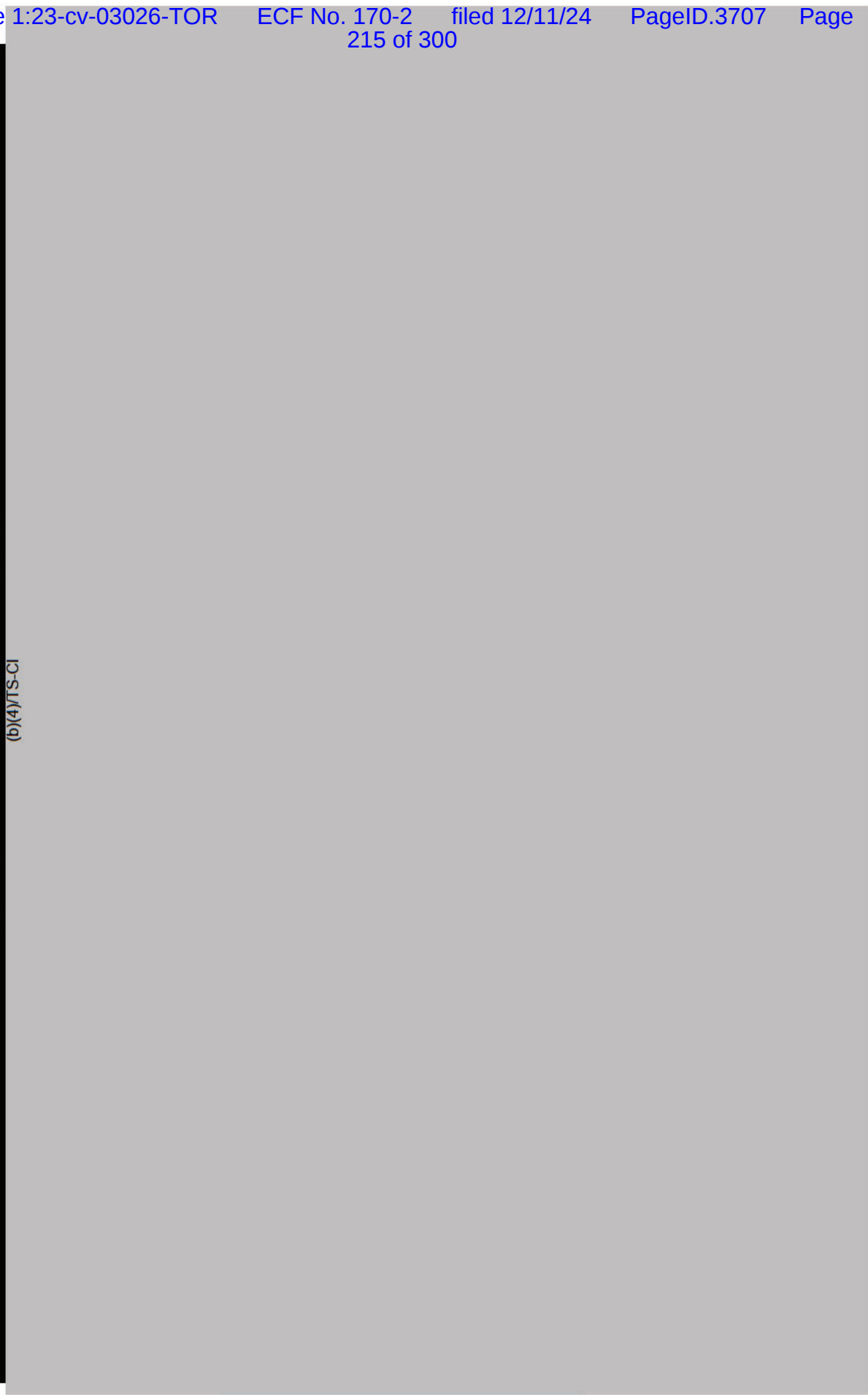
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REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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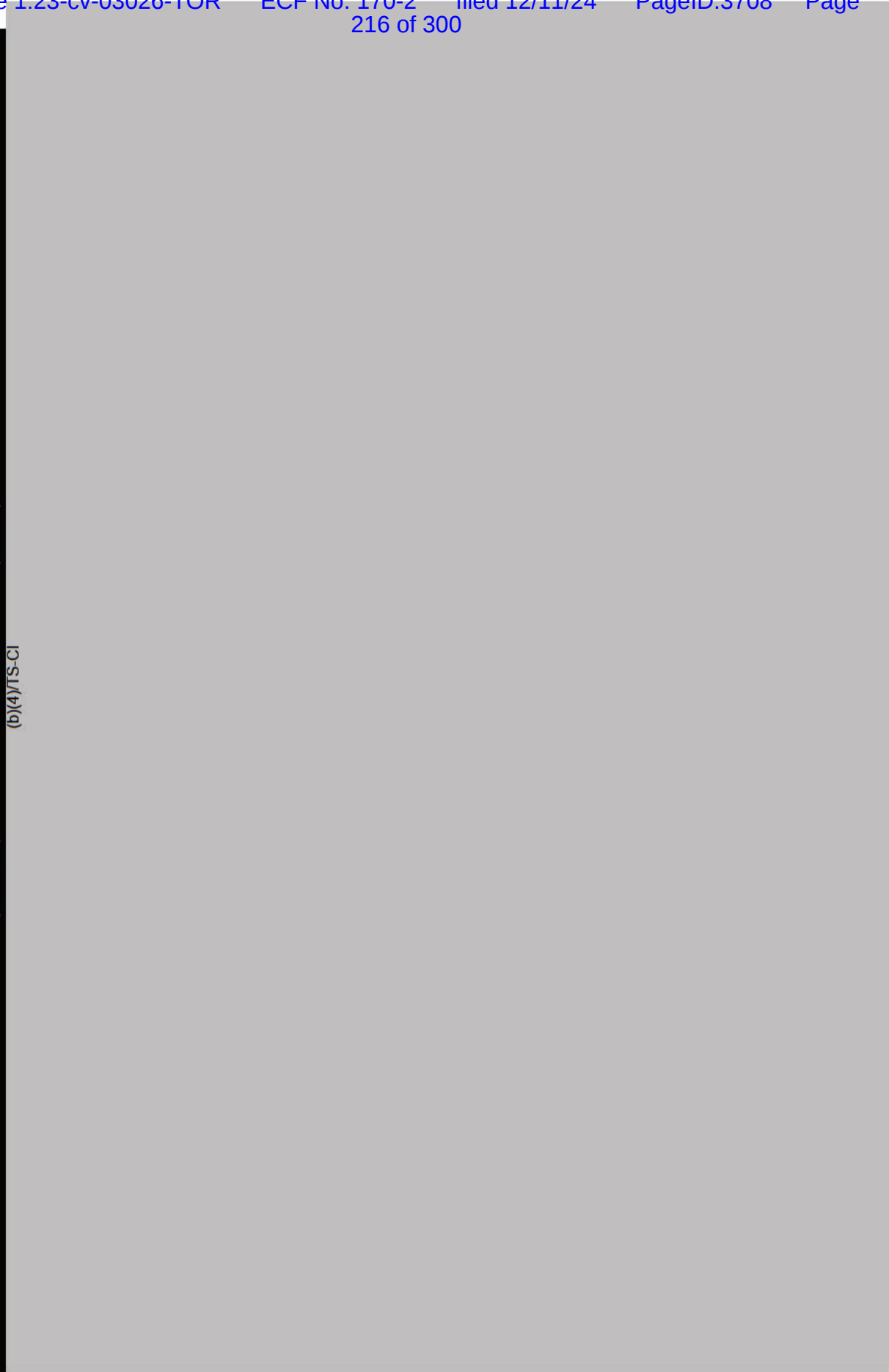
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REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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JUN18 FINAL - FINAL

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REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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REMS Modification Comparison

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CURRENT REMS	PROPOSED REVISIONS (Redline)	PROPOSED REVISIONS (Clean)	REASON FOR MODIFICATION
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REMS Modification Comparison

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REMS Modification Comparison

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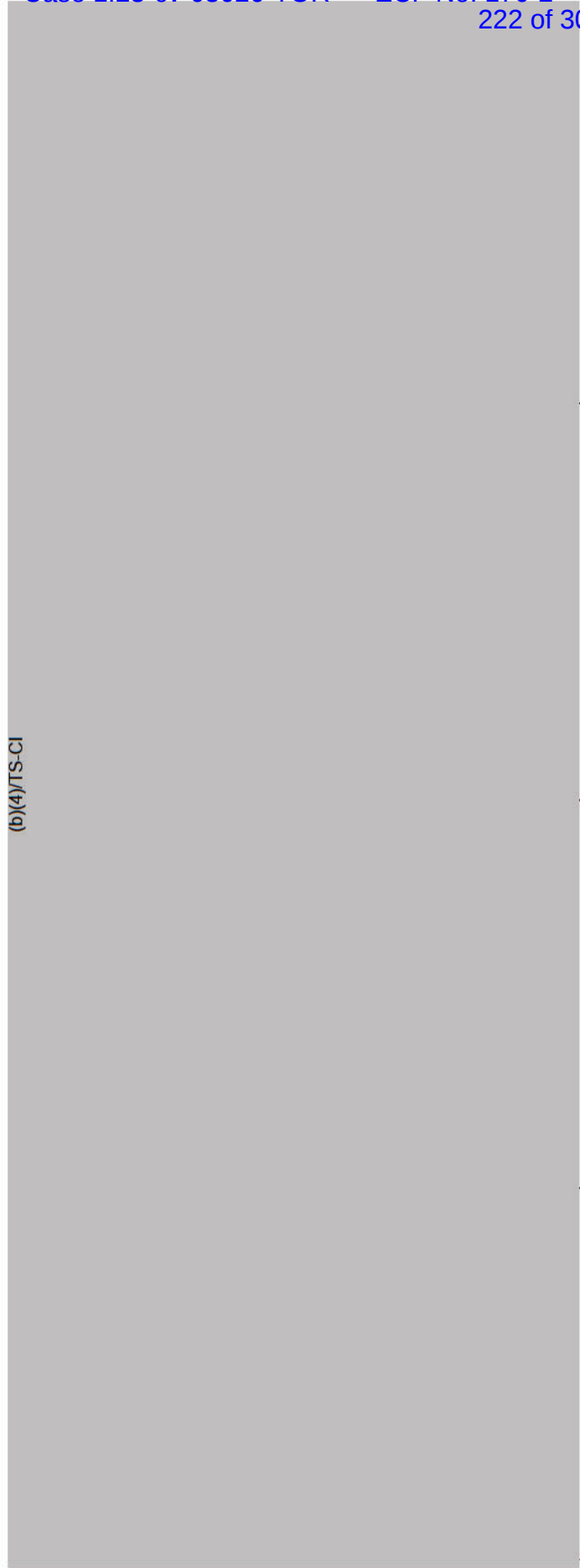
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REMS Modification Comparison

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REMS Modification Comparison

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REMS Modification Comparison

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REMS Modification Comparison

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REMS Modification Comparison

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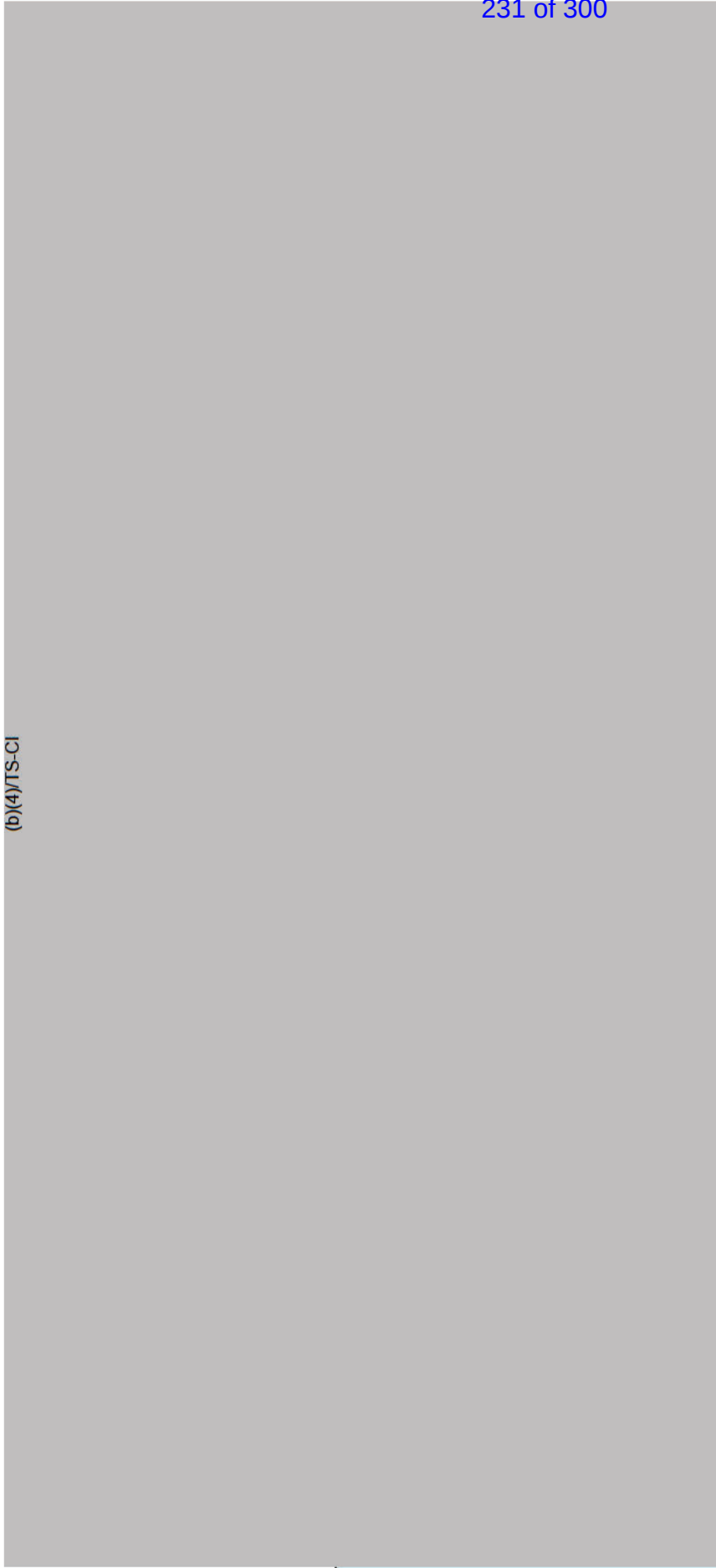
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REMS Modification Comparison

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REMS Modification Comparison

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REMS Modification Comparison

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REMS Modification Comparison

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JUN18 FINAL - FINAL

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## 1.16.2 Summary of the Proposed REMS Modifications

### 1. Introduction

On December 16, 2021, the Agency directed Danco Laboratories, LLC (“Danco”) and GenBioPro, Inc. (“GenBioPro”) (collectively, the “Sponsors”) in a [REMS Modification Notification dated December 16, 2021](#) to modify the Mifepristone SSS REMS (the “REMS”) as follows:

**Elements to Assure Safe Use:** We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”) is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will reduce the burden on the healthcare delivery system of complying with the REMS.

**Elements to Assure Safe Use:** Pursuant to §505-1(f)(1) [of the Food, Drug, and Cosmetic Act], we have also determined that an additional element to assure safe use is necessary to mitigate the risk of serious complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers who prescribe the drugs have particular experience or training, or are specially certified[.]
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified[.]
- The drug is dispensed to patients with evidence or other documentation of safe use conditions.

The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

On March 11, 2022, the Sponsors submitted a Type A Meeting Request including questions regarding the REMS Modification to which the Agency provided [Written Responses on April 8, 2022](#).

GenBioPro and Danco have worked collaboratively to modify the REMS for mifepristone as directed by FDA.

This document summarizes and provides further explanation for the proposed Modifications to the mifepristone REMS and serves as the adequate rationale for the REMS Modifications to the extent required by § 505-1(g)(4)(A) of the Food, Drug, and Cosmetic Act (FDCA). Additionally, a detailed [side-by-side annotated comparison of the proposed modified REMS versus the approved REMS](#) is provided in Section 1.16.2.2.

## 2. Background

Based on FDA's review of published literature, safety information collected during the ongoing COVID-19 public health emergency, FDA Adverse Event Reporting Systems (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, and parties in ongoing litigation, FDA determined that the in-person dispensing requirement is no longer necessary to ensure the benefit of the drug outweigh the risk and that modification of the REMS to add pharmacy certification is necessary to allow dispensing by pharmacies.

The proposed Modifications to the REMS and REMS materials were developed to allow for mifepristone to be prescribed by certified prescribers (b)(4)/TS-CI without imposing in-person assessment, counseling, consenting, prescribing or follow-up requirements. In addition, the proposed Modifications provide for mifepristone to be dispensed by mail/courier (as well as in person) by or under the supervision of certified prescribers or by certified pharmacies, while meeting the statutory requirement under §505-1(f)(2)(B) of the FDCA to minimize the burden on the health care system and not be unduly burdensome on patient access to the drug (especially to patients who have difficulty accessing health care, such as patients in rural or medically underserved areas or who have other limitations).

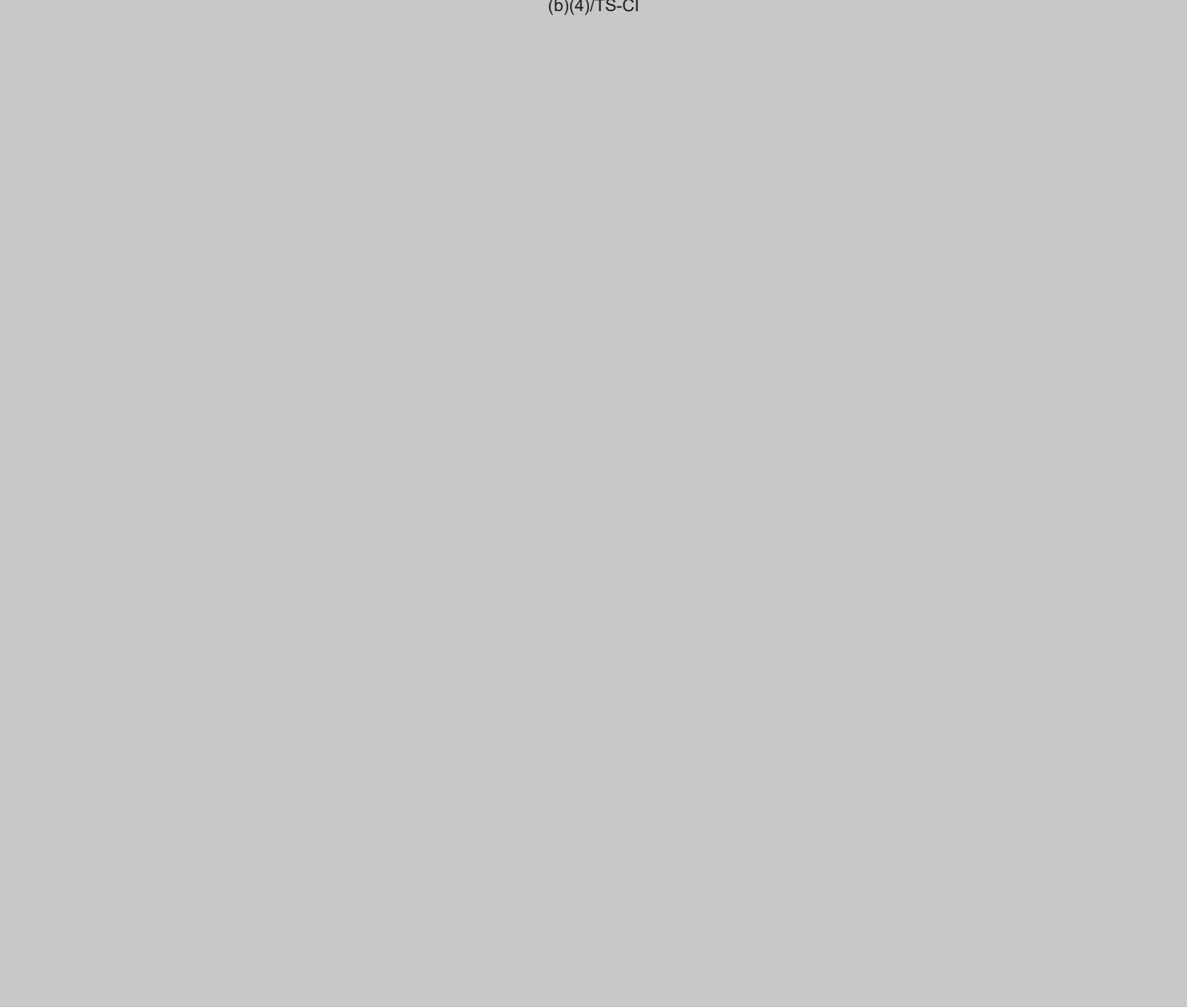
In developing the modified REMS, the Sponsors considered both the FDA's responses (in its [Written Response](#)) to the Sponsors' questions and their extensive experience with the use and distribution of mifepristone, including the experience gained over the last two years with the provision of mifepristone through telemedicine and mail delivery by healthcare providers and mail-order pharmacies. They have also consulted with a broad range of stakeholders, including current and potential prescribers, mail and retail pharmacies, distributors, and other experts to develop REMS Modifications that would best meet the FDA directive to improve access and maintain safe use without imposing undue burdens on patients and stakeholders.

The Sponsors' proposed REMS includes several interrelated elements to implement the REMS to meet the Agency's objectives and mandate under §505-1(f)(2)(B) while avoiding the unintended effect of limiting access, increasing burdens, and introducing risks to healthcare provider and patient confidentiality. In that regard, the proposed modified REMS is intended to meet the applicable legal standards and reflect FDA's considered view of what conditions are necessary for the safe use of mifepristone for the intended use, such that additional restrictions would be

inconsistent with the conditions of use (including its labeling, distribution, prescribing, dispensing and use) established by the Agency under its unique and exclusive statutory authority, mandates and recognized expertise. We ask FDA to carefully evaluate our proposed Modifications, as a suitable approach to assure that patient access to mifepristone under such restrictions as necessary to safe use.

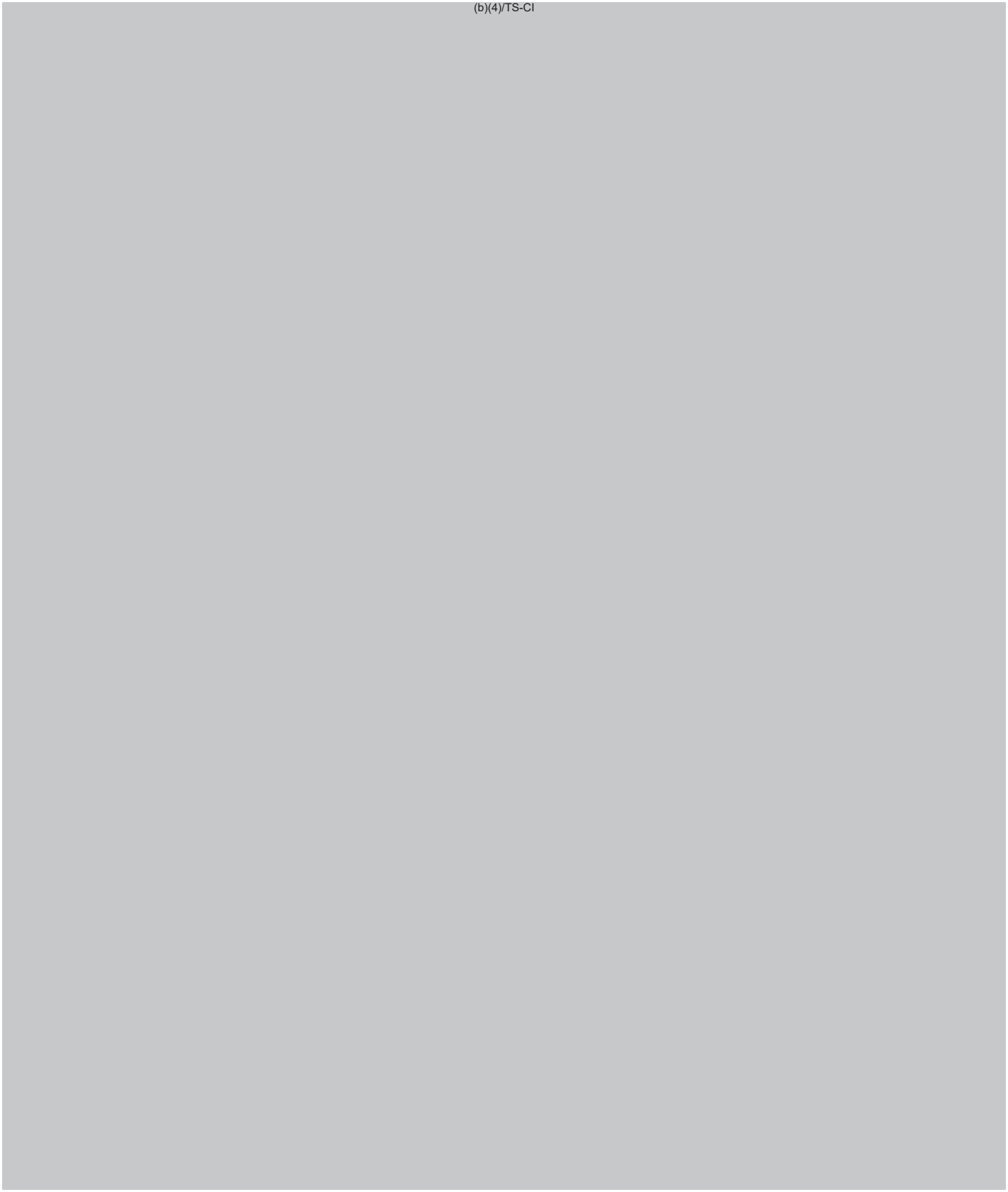
The proposed Modified REMS includes the following:

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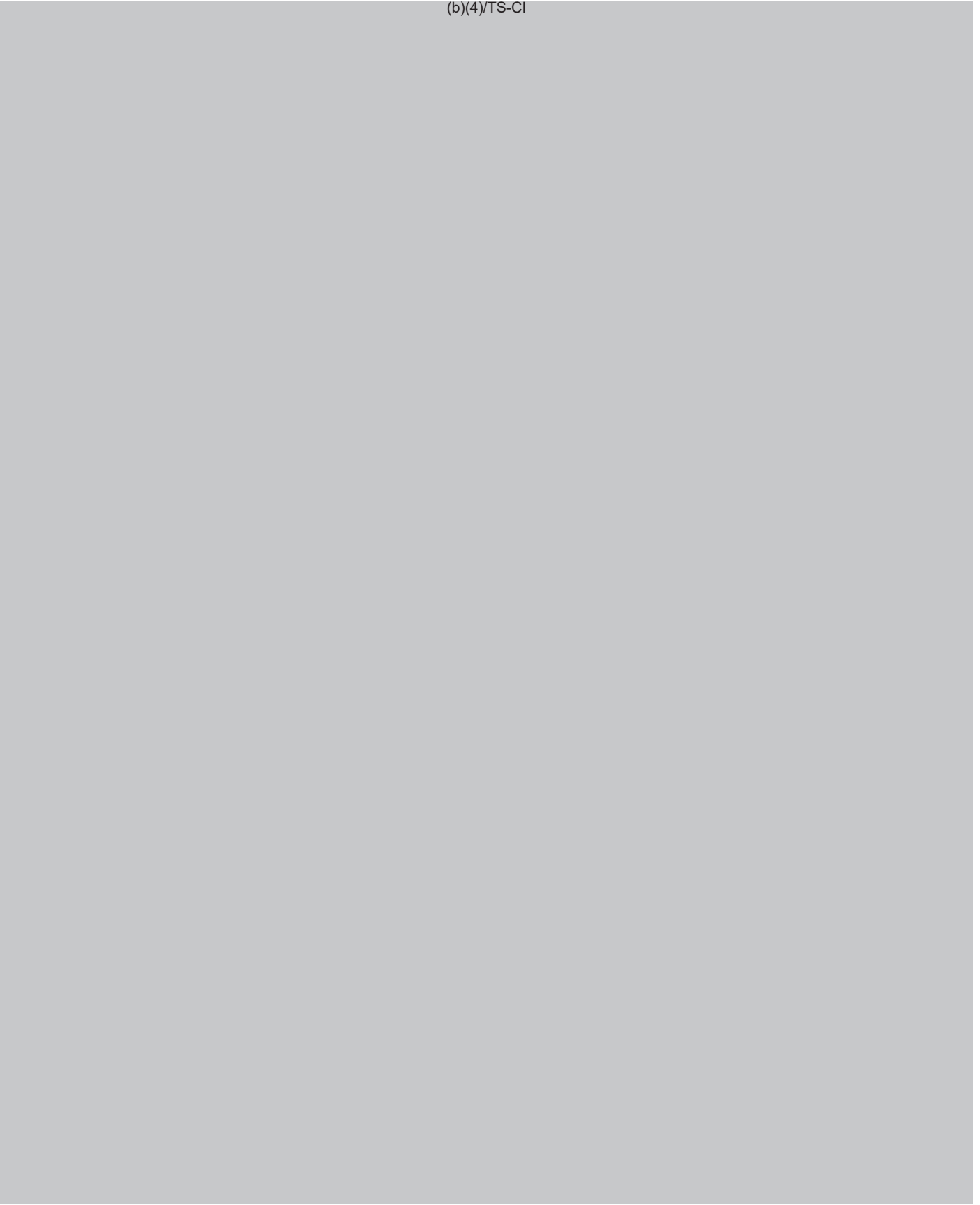
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Center for Drug Evaluation and Research (CDER)

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<b>Application Type</b>	NDA and ANDA
<b>Application Number</b>	NDA 020687 and ANDA 091178
<b>Supplement Number, Date Received</b>	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequences 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022 (sequences 24 and 92 respectively), December 9, 2022 (sequences 25 and 93 respectively) and December 16, 2022 (sequences 26 and 95 respectively). This supplement is on a 180-Day clock.
<b>Targeted Action Date</b>	December 19, 2022
(b) (6) #	2022-1169
<b>Reviewer Names</b>	(b) (6) (b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
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<b>Review Completion Date</b>	January 3, 2023
<b>Subject</b>	Review of proposed Major REMS Modification
<b>Established Name</b>	Mifepristone REMS
<b>Name of Sponsor</b>	Danco Laboratories, LLC and GenBioPro, Inc.
<b>Therapeutic Class</b>	Progestin antagonist
<b>Formulation</b>	Oral tablet

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## EXECUTIVE SUMMARY

This is a review of the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178. The Sponsors submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, and amended their submissions on October 19, 2022 (Danco), October 20, 2022 (GBP), November 30, 2022 (both), December 9, 2022 (both) and December 16, 2022 (both).

The Mifepristone REMS Program was originally approved on April 11, 2019, to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021.<sup>a</sup> The Mifepristone REMS Program consists of elements to assure safe use (ETASU) A, C and D, an implementation system, and a timetable for submission of assessments of the REMS.

The Sponsors submitted the proposed modification to the REMS in response to the Agency's REMS Modification Notification letters dated December 16, 2021, which required removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") and the addition of certification of pharmacies that dispense the drug.

In addition, the following were addressed during the course of the review:

- revisions to the REMS goal to align with the updated REMS requirements.
- replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms, Patient Agreement Form, and Pharmacy Agreement Forms*).

The review team finds the proposed modification to the Mifepristone REMS Program last submitted on December 16, 2022, to be acceptable and recommends approval of the REMS modification. The proposed REMS modification includes changes to the REMS goal, additional REMS requirements for prescribers to incorporate dispensing from certified pharmacies and new REMS requirements for pharmacy certification.

The proposed goal of the modified REMS for mifepristone 200 mg is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

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<sup>a</sup> The May 14, 2021 REMS modification approved the inclusion of gender neutral language in the Patient Agreement Form as well as corresponding minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

The timetable for submission of assessments of the REMS was modified to one year from the date of the approval of the modified REMS and annually thereafter. The assessment plan was revised to align with the changes to the REMS and capture additional metrics for drug utilization and REMS operations.

The modified REMS includes ETASU A, B and D, an implementation system, and a timetable for submission of assessments of the REMS. Mifepristone will no longer be required to be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the “in-person dispensing requirement” for brevity) and will be able to be dispensed from certified pharmacies.

## 1. Introduction

This review evaluates the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Sponsors initially submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, in response to the Agency’s REMS Modification Notification letters issued on December 16, 2021, to Danco and GBP, requiring the following modification to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”)
- addition of certification of pharmacies that dispense the drug

Per the Agency’s December 16, 2021, REMS Modification Notification letters, the proposed REMS was required to include the following ETASU to mitigate the risk of serious complications associated with mifepristone, including at least the following:

- healthcare providers have particular experience or training, or are specially certified
- pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- the drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS was also required to include an implementation system and timetable for submission of assessments.

## 2. Background

### 2.1. Product Information and REMS Information

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H)<sup>b</sup> to ensure that the benefits of the drug outweighed

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<sup>b</sup> NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

the risk of serious complications associated with mifepristone when used for medical abortion.<sup>c</sup> Mifeprex was deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and the Mifeprex REMS was approved on June 8, 2011.

On March 29, 2016, FDA approved an efficacy supplement for Mifeprex, which included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol, as well as a modification of the gestational age up to which Mifeprex has been shown to be safe and effective and a modification to the process for follow-up after administration of the drug. FDA also approved modification to the Mifeprex REMS that reflected the changes approved in the efficacy supplement.<sup>1-5</sup> On April 11, 2019, FDA approved ANDA 091178 and the Mifepristone REMS Program.<sup>6-7</sup> The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 091178. The goal of the approved Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
- b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber (under ETASU C).
- c) Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

The Mifepristone REMS Program was last modified and approved in 2021 to revise the *Patient Agreement Form* to include gender-neutral language; however, the goal of the Mifepristone REMS Program has not changed since the initial approval in 2019.

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form*, and agree to follow the guidelines for use of mifepristone. Under ETASU C, in the Mifepristone REMS Program as approved prior to today's action, mifepristone was required to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The approved Mifepristone REMS Program includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public health emergency (PHE) regarding the in-person dispensing requirement in the Mifepristone REMS Program. Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020, to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.<sup>8</sup>

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<sup>c</sup> Mifepristone is also approved in approximately 80 other countries.  
[https://gynuity.org/assets/resources/biblio\\_ref\\_lst\\_mife\\_en.pdf](https://gynuity.org/assets/resources/biblio_ref_lst_mife_en.pdf)

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

## 2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 04/11/2019: Approval of the Mifepristone REMS Program, a single, shared system REMS that includes NDA 020687 and ANDA 091178.
- 04/12/2021: The Agency issued a General Advice letter to both the NDA and ANDA Applicants, explaining that FDA intended to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.
- 05/07/2021: The Agency stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with section 505-1 of the FD&C Act.
- 12/16/2021: The Agency completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification.<sup>9</sup>
- 12/16/2021: REMS Modification Notification letters were sent to both Sponsors stating that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare system of complying with the REMS and ensure that the benefits of the drug outweigh the risks.
- 04/08/2022: Final written responses to a Type A meeting request were provided to Danco, the point of contact for the Mifepristone REMS Program. The questions pertained to the 12/16/2021 REMS Modification Notification letter requirements.
- 04/13/2022: The Sponsors requested an extension to 6/30/2022, to submit a proposed REMS modification in response to the Agency's 12/16/2021 REMS Modification Notification letters.
- 04/15/2022: The Agency granted the Sponsors' request for an extension to submit a proposed REMS modification and conveyed that the modification must be submitted no later than 06/30/2022.<sup>10</sup>
- 06/22/2022: Danco and GBP submitted a proposed REMS modification to their respective applications in response to the 12/16/2021 REMS Modification Notification letters.
- 07/22/2022: An Information Request was sent to the Sponsors requesting clarification of the proposed prescriber and dispenser requirements and additional rationale to support their proposal.
- 08/26/2022: Sponsors submitted responses to 07/22/2022 Information Request.
- 09/19/2022: Teleconference was held between Agency and Sponsors where the Agency communicated the REMS requirements that are necessary to support the addition of pharmacy

certification. The Agency proposed focusing on the pharmacy settings where a closed system<sup>d</sup> REMS could be implemented using the existing email and facsimile based system, (b) (4), as the best strategy for an approvable modification by the goal date.

- 09/22/2022: An Information Request was sent to Sponsors requesting confirmation that the Sponsors agree with the pharmacy distribution approach outlined in the 09/19/2022 teleconference so that the Agency's feedback could be appropriately tailored.
- 09/23/2022: The Sponsors confirmed via email that they were willing to pursue (b) (4), as discussed in the 09/19/2022 teleconference. The Sponsors also requested a teleconference to discuss the current modification (b) (4).
- 09/27/2022: Comments from the 09/19/2022 teleconference sent to Sponsors with additional comments and requests regarding what will be necessary for pharmacy certification.
- 09/29/2022: An Information request was sent to the Sponsors asking for agenda items, questions, and a request to walk through their proposed system for pharmacy certification, including dispensing through mail-order or specialty pharmacies, at the 10/06/2022 scheduled teleconference.
- 10/04/2022: Sponsors emailed that they will focus the 10/06/2022 teleconference on the 09/27/2022 Agency comments and their mail order and specialty pharmacy distribution model.
- 10/06/2022: Teleconference was held between Agency and Sponsors where Sponsors outlined their proposal for pharmacy certification, including dispensing through mail order and specialty pharmacies, as well as their concerns with certain requirements and general timelines.
- 10/19/2022: Danco submitted a REMS amendment to their pending sNDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/20/2022: GBP submitted a REMS amendment to their pending sANDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/25/2022: Teleconference was held between Agency and Sponsors to discuss the *Patient Agreement Form* and timing related to shipping a mifepristone prescription from a certified pharmacy to the patient.
- 11/23/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document, submitted on 10/19/2022 (Danco) and 10/20/2022 (GBP).
- 11/30/2022: Danco and GBP submitted REMS amendments, which included the REMS Document, to their respective pending supplemental applications.
- 12/01/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document.
- 12/05/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document submitted on 11/30/2022 and discussed at the teleconference on 12/01/2022, and REMS materials submitted to their applications on 10/19/2022 and 10/20/2022.

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<sup>d</sup> "Closed system" in this case refers to a system where prescribers, pharmacies, and distributors are certified or authorized in the REMS and the certification of the stakeholder must be verified prior to distribution or dispensing, as per the REMS.

- 12/07/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document and REMS materials the Agency sent to the Sponsors on 12/05/22.
- 12/08/2022: Danco and GBP submitted REMS amendments, including the REMS Document, *Prescriber Agreement Form*, *Pharmacy Agreement Form*, *Patient Agreement Form* and REMS Supporting Document, to their respective pending applications.
- 12/09/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS assessment plan.
- 12/14/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS Document, *Prescriber Agreement Form*, *Pharmacy Agreement Form*, and REMS Supporting Document.
- 12/15/2022: Two teleconferences were held between Agency and Sponsors to discuss the proposed REMS Document and REMS materials the Agency sent to the Sponsors on 12/14/22.
- 12/16/2022: Sponsors submitted a REMS amendment to their respective applications.

### 3. Review of Proposed REMS Modification

(b) (6) has discussed the Sponsors' proposed modification with the review team, which includes members of the (b) (6) and the (b) (6); hereafter referred to as the review team. This review includes their input and concurrence with the analysis and proposed changes to the Mifepristone REMS Program.

#### 3.1. REMS Goal

The Sponsors proposed modification to the goal for the Mifepristone REMS Program to add that mifepristone can also be dispensed from certified pharmacies on prescriptions issued by certified prescribers. The proposed REMS goal is:

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

**Reviewer Comment:** *We agree with the Sponsors' proposal.*

#### 3.2. REMS Document

The proposed REMS Document is not in the format as outlined in the 2017 Draft Guidance for Industry, Format and Content of a REMS Document.<sup>11</sup>

**Reviewer Comment:** *To avoid the misperception that this REMS modification is making major changes to the REMS document that go beyond our December 16, 2021, determination that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification, CDER staff and management discussed whether to change the format of the REMS document to that described in the 2017 draft guidance.<sup>11</sup> After internal discussion, CDER staff and management aligned not to transition the REMS document at this time to the format described in the 2017 draft guidance.*

### **3.3. REMS Requirements**

#### **3.3.1. Addition and Removal of ETASU**

The December 16, 2021, REMS Modification Notification letters specified that the ETASU must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure the benefits of the drug outweigh the risks by:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices and hospitals (i.e., the “in-person dispensing requirement”), and;
- Adding a requirement that pharmacies that dispense the drug be specially certified.

The Sponsors proposed changes to the REMS as reflected in the subsections below.

#### **3.3.2. REMS Participant Requirements and Materials**

##### **3.3.2.1. Prescriber Requirements**

Consistent with the approved Mifepristone REMS Program prescribers must be specially certified. To become specially certified to prescribe mifepristone, healthcare providers who prescribe must review the Prescribing Information for mifepristone and complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet certain qualifications and will follow the guidelines for use of mifepristone. The guidelines for use include ensuring i) that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained; ii) that the healthcare provider (HCP) and the patient sign the *Patient Agreement Form*, iii) the patient receives a copy of the *Patient Agreement Form* and Medication Guide, iv) the *Patient Agreement Form* is placed in the patient’s medical record; v) that any patient deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient. The language on the guidelines for use was revised from the Mifepristone REMS Program approved in 2021 to clarify that, if the certified prescriber supervises the dispensing of mifepristone, they must ensure the guidelines for use of mifepristone are followed by those under their supervision. This clarification reflects the ongoing implementation of the approved Mifepristone REMS Program. For example, consistent with the approved REMS, the *Patient Agreement Form* does not require the certified prescriber’s signature, but rather the signature of the healthcare provider counseling the patient on the risks of mifepristone. Additional changes were made globally to provide consistency and clarity of the requirements for certified prescribers and healthcare providers who complete tasks under the supervision of certified prescribers.

A certified prescriber may submit the *Prescriber Agreement Form* to an authorized distributor if the certified prescriber wishes to dispense or supervise the dispensing of mifepristone; this is consistent with the current requirements of the Mifepristone REMS Program. Additional requirements were

added to incorporate mifepristone dispensing by a certified pharmacy. If a healthcare provider wishes to prescribe mifepristone by sending a prescription to a certified pharmacy for dispensing, the healthcare provider must become certified by providing the pharmacy a *Prescriber Agreement Form* signed by the provider. A certified prescriber must also assess the appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy.

The NDC and lot number of the dispensed drug will be recorded in the patient's record when mifepristone is dispensed by or under the supervision of a certified prescriber, replacing the requirement that serial numbers from each package of mifepristone be recorded in the patient's record. If prescribers become aware of the death of a patient for whom the mifepristone was dispensed from a certified pharmacy, the prescribers will be required to obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy.

The following materials support prescriber requirements:

- *Prescriber Agreement Form* for Danco Laboratories, LLC
- *Prescriber Agreement Form* for GenBioPro, Inc.
- *Patient Agreement Form*

**Reviewer Comment:** *We agree with the Sponsors' proposal.*

*Although certain activities (review of the Patient Agreement Form with patients and answering any questions about treatment, signing, providing a copy to the patient and retaining the Patient Agreement Form, providing a copy of the Medication Guide, and ensuring any deaths are reported to the Mifepristone Sponsor, recording the NDC and lot number from drug dispensed from the certified prescriber or those under their supervision) may be conducted by healthcare providers under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. We agree with the additional language to further clarify that the certified prescriber must ensure the guidelines for use of mifepristone are followed.*

*As proposed, certified prescribers may either, 1) continue to submit the Prescriber Agreement Form to an authorized distributor if the certified prescriber is dispensing or supervising the dispensing of the drug (as already required in the REMS), or 2) if the drug will be dispensed from a certified pharmacy, submit the Prescriber Agreement Form to the certified pharmacy that will dispense the drug (as proposed in the modification). Regarding #2, the pharmacy can only fill prescriptions written by a certified prescriber.*

*Based on our review of the proposed changes, the review team finds it acceptable for prescribers to submit their Prescriber Agreement Form directly to the certified pharmacy. Although certified prescribers still have the option of in-person dispensing of the drug, not all prescribers may want to stock mifepristone. Typically due to the number of drugs that are available and the expense associated with stocking prescription medications intended for outpatient use, most prescribers do not stock many medications, if they stock medications at all.*

*The proposal to submit a Prescriber Agreement Form to a certified pharmacy provides another option for dispensing mifepristone. The burden of providing the Prescriber Agreement Form prior to or when the prescription is provided to a certified pharmacy does not create unreasonable burden for prescribers. The burden of prescriber certification has been minimized to the extent possible. The Prescriber Agreement Form is designed to require minimal time to complete and requires that the prescriber submit it to the authorized distributor once, and if the prescriber chooses to use a certified pharmacy to dispense mifepristone, they will need to submit the form to the certified pharmacy.*

*There is an additional requirement added for certified pharmacies and certified prescribers in the event that a patient will not receive their medication from the certified pharmacy within four calendar days of the pharmacy's receipt of the prescription (for example, if the medication is not in stock). In this circumstance, the pharmacy will be required to contact the certified prescriber to make them aware of the delay and will be required to obtain from the prescriber confirmation that it is appropriate to dispense mifepristone to the patient even though they will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy. This confirmation is intended to ensure timeliness of delivery in light of the labeled indication and gestational age. Additional details and rationale on the pharmacy requirements to dispense and ship drug in a timely manner are described in section 3.3.2.3.*

*If a certified prescriber becomes aware of a patient death that occurs subsequent to the use of mifepristone dispensed from a pharmacy, the certified prescriber must obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy. This information will be reported to the appropriate Mifepristone Sponsor in the same manner prescribers have done previously. This additional requirement to obtain the NDC and lot number from the pharmacy is needed to ensure consistent adverse event reporting when mifepristone is dispensed from a certified pharmacy.*

#### Prescriber Agreement Form

The Sponsors' proposed changes to the *Prescriber Agreement Form* aligned with those described above. The proposed *Prescriber Agreement Form* explains the two methods of certification which are: 1) submitting the form to the authorized distributor and 2) submitting the form to the dispensing certified pharmacy. Further clarification was added that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification. The statement that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program was also added. The following statement was added to the form: "I understand that the pharmacy may dispense mifepristone made by a different manufacturer than that stated on the Prescriber Agreement Form." The account set up information was removed and replaced with prescriber information response fields.

**Reviewer Comment:** *We agree with the Sponsors' proposal. Changes in the above prescriber requirements were incorporated in the Prescriber Agreement Form.*

### **3.3.2.2. Patient Requirements**

The *Patient Agreement Form* was updated to clarify that the signatures may be written or electronic, to reorganize the risk information about ectopic pregnancy, and to remove the statement that the Medication Guide will be taken to an emergency room or provided to a healthcare provider who did not prescribe mifepristone so that it is known that the patient had a medical abortion with mifepristone.

The following materials support patient requirements:

- *Patient Agreement Form*

**Reviewer Comment:** *We agree with the Sponsors' proposal.*

*The Patient Agreement Form continues to be an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the*

*patient, to provide the patient with the Patient Agreement Form, and to have the healthcare provider and patient sign the Patient Agreement Form, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The form is signed by the patient and the provider and placed in the patient's medical record, and a copy is provided to the patient, to document the patient's acknowledgment of receiving the information from the prescriber. The Agency agrees that the further clarification that signatures can be written or electronic is appropriate for the continued use of the form.*

*The reference to ectopic pregnancy has been reorganized in the document since it is not a risk of the drug. The signs and symptoms of an untreated ectopic pregnancy that may persist after mifepristone use have been clarified in the section of the form that explains the signs and symptoms of potential problems that may occur after mifepristone use.*

*The review team agrees with removing the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion. Although this statement has been in the Medication Guide for a number of years, upon further consideration, the Agency has concluded that patients seeking emergency medical care are not likely to carry a Medication Guide with them, the Medication Guide is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.*

### **3.3.2.3. Pharmacy Requirements**

The Sponsors proposed that certified pharmacies, in addition to certified prescribers and HCPs under the supervision of certified prescribers, can dispense mifepristone. In order for a pharmacy to become certified, the pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy. The Authorized Representative must certify that they have read and understood the Prescribing Information for mifepristone. Each location of the pharmacy must be able to receive *Prescriber Agreement Forms* by email and fax and be able to ship mifepristone using a shipping service that provides tracking information.

Additionally, each dispensing pharmacy location must put processes and procedures in place to fulfill the REMS requirements. Certified pharmacies must verify prescriber certification by confirming they have obtained a copy of the prescriber's signed *Prescriber Agreement Form* before dispensing. Certified pharmacies must dispense mifepristone such that it is received by the patient within four days from the day of prescription receipt by the pharmacy. If the pharmacy will not be able to deliver mifepristone to the patient within four days of receipt of the prescription, the pharmacy must contact the prescriber to confirm the appropriateness of dispensing mifepristone and document the certified prescriber's decision. The pharmacy must also record the NDC and lot number from each package of mifepristone dispensed in the patient's record, track and verify receipt of each shipment of mifepristone, dispense mifepristone in its original package, and only distribute, transfer, loan, or sell mifepristone to certified prescribers or between locations of the certified pharmacy. The pharmacy must also report any patient deaths to the prescriber, including the NDC and lot number from the package dispensed to the patient, and remind the prescriber of their obligation under the REMS to report patient deaths to the Sponsor that supplied the mifepristone; the certified pharmacy also must notify the Sponsor that supplied the mifepristone that the pharmacy submitted a report of a patient death to the prescriber and include the name and contact information for the prescriber as well as the NDC and lot number of the dispensed

product. Record-keeping requirements of the pharmacy include records of *Prescriber Agreement Forms*, mifepristone dispensing and shipping, and all processes and procedures and compliance with those processes and procedures. Pharmacies must train all relevant staff and participate in compliance audits. Pharmacies must also maintain the identity of patients and providers as confidential, including limiting access to patient and provider identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes. The requirement that mifepristone not be dispensed from retail pharmacies was removed.

The following materials support pharmacy requirements:

- *Pharmacy Agreement Form* for Danco Laboratories, LLC
- *Pharmacy Agreement Form* for GenBioPro, Inc.

**Reviewer Comment:** *We agree with the Sponsors' proposal. The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, mifepristone can be dispensed from a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that the prescriber is certified prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the Patient Agreement Form is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review and our consideration of the distribution model implemented by the Sponsors during the periods when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients.*

*The requirement to maintain confidentiality, including limiting access to patient and provider identity only to those personnel necessary for dispensing under the Mifepristone REMS Program or as necessary for payment and/or insurance purposes, is included to avoid unduly burdening patient access.*

*The Sponsors proposed inclusion of this requirement because of concerns that patients may be reluctant or unwilling to seek to obtain mifepristone from pharmacies if they are concerned that confidentiality of their medical information could be compromised, potentially exposing them to intimidation, threats, or acts of violence by individuals opposed to the use of mifepristone for medical abortion.<sup>e</sup> Further, unwillingness on the part of prescribers to participate in the Mifepristone REMS Program on the basis of*

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<sup>e</sup> See e.g., *2020 Violence and Disruption Statistics*, National Abortion Federation (Dec. 16, 2021), <https://prochoice.org/national-abortion-federation-releases-2020-violence-disruption-statistics/>; Amanda Musa, CNN, *Wyoming Authorities Search for a Suspect Believed to Have Set an Abortion Clinic on Fire*, CNN WIRE (June 10, 2022), <https://abc17news.com/news/2022/06/10/wyoming-authorities-search-for-a-suspect-believed-to-have-set-an-abortion-clinic-on-fire/>.

*similar confidentiality concerns may unduly burden patient access by limiting the number of prescribers who are willing to send prescriptions to certified pharmacies. Addition of this requirement protects patient access by requiring the pharmacy to put processes and procedures in place to limit access to confidential information to only those individuals who are essential for dispensing mifepristone under the Mifepristone REMS Program or as necessary for payment or insurance purposes. Inclusion of this requirement for certified pharmacies is consistent with the requirement in the current Mifepristone REMS Program, that distributors maintain secure and confidential records.*

*Reference to mifepristone not being available in retail pharmacies was removed from the REMS. There is no single definition of the term "retail pharmacy" and therefore the scope of the exclusion in the REMS was not well defined. Including a restriction in the Mifepristone REMS Program that retail pharmacies cannot participate in the REMS may unintentionally prohibit the participation of mail order and specialty pharmacies that could, under one or more definitions, also be considered a "retail pharmacy."*

*After reconsideration of the term, "retail," the Agency concluded that a more appropriate approach was to articulate the specific requirements that would be necessary for pharmacy certification. As modified, the REMS will not preclude the participation of any pharmacy that meets the certification requirements. However, we acknowledge that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS. The REMS requires that pharmacies dispense mifepristone only after verifying that the prescriber is certified. The REMS further requires that pharmacies be able to receive the Prescriber Agreement Forms by email and fax.*

(b) (4)

*The pharmacy certification requirements include that the drug reach patients within four days of the certified pharmacy receiving the prescription. During the course of the review, the review team concluded that requiring medication delivery to the patient within four days of the pharmacy's receipt of a prescription is acceptable based on the labeled indication and literature,<sup>13</sup> while taking into account practical shipping considerations (e.g., shipping over weekends and holidays). For patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription, the pharmacy must notify the certified prescriber and the certified prescriber must determine if it is still appropriate for the certified pharmacy to dispense the drug. The pharmacy must document the certified prescriber's decision. A prescriber's confirmation that it is appropriate to dispense mifepristone when it will not be delivered to the patient within the allotted four days is intended to ensure timeliness of delivery in light of the labeled indication and gestational age.*

#### Pharmacy Agreement Form

The proposed *Pharmacy Agreement Form* is a new form and is the means by which a pharmacy becomes certified to dispense mifepristone. The form, which is submitted by an authorized representative on behalf of a pharmacy seeking certification, outlines all requirements proposed above. Clarification is included in the form that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program, do not require pharmacy certification. Any new authorized representative must complete and submit the *Pharmacy Agreement Form*. Spaces for specific authorized representative information and pharmacy name and address are included. The completed form can be submitted by email or fax to the authorized distributor.

**Reviewer Comment:** *We agree with the Sponsors' proposal. The Pharmacy Agreement Form aligns with the pharmacy requirements discussed above.*

#### **3.3.2.4. Distributor Requirements**

The Sponsors proposed that the distributors' processes and procedures in the approved Mifepristone REMS Program be updated to ensure that mifepristone is only shipped to clinics, medical offices and hospitals identified by certified prescribers and to certified pharmacies. Distributors will continue to complete the certification process for any *Prescriber Agreement Forms* they receive and also will complete the certification process for pharmacies upon receipt of a *Pharmacy Agreement Form*, including notifying pharmacies when they become certified. FDA was removed as a potential auditor for distributors.

**Reviewer Comment:** *We agree with the Sponsors' proposal. At this time, FDA does not audit distributors directly, it carries out inspections of Sponsors to monitor industry compliance with REMS requirements.*

#### **3.3.3. REMS Sponsor Requirements**

##### **3.3.3.1. Sponsor Requirements to Support Prescriber Certification**

The Sponsors proposed additions to this section of the REMS document, including that Sponsors will ensure prescribers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy, and that Sponsors will ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date. Sponsors will also ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*: (1) within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies, or (2) within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

**Reviewer Comment:** *We agree with the Sponsors' proposal. The requirement to confirm that the locations associated with the certified prescriber are current is parallel to the pharmacy requirement that the authorized representative's contact information is up to date. In determining the pharmacy requirement, which is necessary to ensure program compliance and is consistent with other approved REMS that include pharmacy certification, the Agency also concluded that a parallel requirement for certified prescribers should be added.*

*With respect to recertification, it is important that active certified prescribers are informed of and agree to new REMS requirements to ensure the continued safe use of mifepristone. There is minimal burden to recertification and the timelines allow sufficient time to accomplish recertification.*

### **3.3.3.2. Sponsor Requirements to Support Pharmacy Certification**

The Sponsors proposed the addition of Sponsor requirements to support pharmacy certification and compliance, including ensuring that pharmacies are certified in accordance with the requirements in the Mifepristone REMS Program, de-certifying pharmacies that do not maintain compliance with the certification requirements, and ensuring that pharmacy certification can be completed by email and fax to an authorized distributor. Annually, the authorized representative's name and contact information will be verified to ensure it corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, a new authorized representative must certify for the pharmacy. All reference to the requirement in the 2021 Mifepristone REMS Program that mifepristone to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber, and not from retail pharmacies, was removed.

**Reviewer Comment:** *We agree with the Sponsors' proposal. Changes are in line with the REMS Modification Notification letters sent December 16, 2021. Refer to section 3.3.2.3 Reviewer Comments on Pharmacy Certification for rationale for removing the statement that mifepristone is not distributed to or dispensed from retail pharmacies. Ensuring that the authorized representative's contact information is up to date is necessary to ensure that there is always a point person who is responsible for implementing the Mifepristone REMS Program in their pharmacy and can address any changes that are needed if pharmacy audits identify a need for improvement.*

### **3.3.3.3. Sponsor Implementation Requirements**

The Sponsors proposed that they will ensure that adequate records are maintained to demonstrate that REMS requirements have been met (including but not limited to records of mifepristone distribution, certification of prescribers and pharmacies, and audits of pharmacies and distributors), and that the records must be readily available for FDA inspections. The distributor audit requirement was updated to audit new distributors within 90 calendar days of becoming authorized and annually thereafter (a one-time audit requirement was previously required). The Sponsors also proposed a pharmacy audit requirement whereby certified pharmacies that order mifepristone are audited within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter for pharmacies that ordered in the previous 12 months.

**Reviewer's Comment:** *We agree with the Sponsors' proposal.*

*The number of pharmacies that will certify in the REMS is uncertain; therefore, to obtain a reliable sample size for the audits, the Sponsors will need to audit all certified pharmacies within 180 calendar days after the pharmacy places its first order and annually thereafter for pharmacies that have ordered mifepristone in the previous 12 months. Audits performed at 180 days should allow time for establishment and implementation of audit protocols and for the Sponsors to perform the audits. With the addition of more stakeholders (i.e., certified pharmacies), it is also necessary to audit distributors annually to ensure the REMS requirements are followed. The requirement to conduct audits annually may be revisited if assessment data shows that the REMS is meeting its goal.*

## **3.4. REMS Assessment Timetable**

The Sponsors proposed that assessments must be submitted one year from the approval of the modified REMS and annually thereafter, instead of every three years as per the previous requirement.

**Reviewer's Comment:** *We agree with the Sponsors' proposal. With the addition of new pharmacy stakeholders and removal of the in-person dispensing requirement, more frequent assessment after this REMS modification is needed to ensure REMS processes are being followed and that the REMS is meeting its goal. The requirement can be revisited at a later date if assessment data shows that the modified REMS is meeting its goal. The NDA applicant is required to submit assessment reports as outlined in the timetable for submission of assessments. These reports address requirements for the Mifepristone REMS Program. The Sponsors have indicated that some data will be submitted as separate reports when Sponsor-specific information is needed to address the assessment metrics.*

#### 4. Supporting Document

The Sponsors' REMS Supporting Document was substantially updated to include information regarding the proposed modification under review. Background and rationale from the 12/16/21 REMS Modification Notification letters was included. An updated description of the REMS goal and the ETASU was also included to align with the changes in the REMS Document and provide further clarification. Further explanation of prescriber requirements and rationale for various pharmacy requirements was also included.

Regarding implementation of the modified REMS, the Sponsors additionally proposed that pharmacies that received and shipped mifepristone during the Agency's exercise of enforcement discretion during the COVID-19 PHE, that wish to continue to dispense mifepristone, will be required to comply with the pharmacy certification requirements within 120 days of approval of the modified REMS.

The communication strategy to alert current and future prescriber and pharmacy stakeholders was outlined. Distributors, certified prescribers that purchased mifepristone in the last twelve months, and various professional organizations will receive information about REMS changes within 120 days of modification approval. The Sponsors proposed to list pharmacies that agree to be publicly disclosed on their respective product websites but disclosure of this nature is not a requirement of the REMS. The Sponsors indicated that they anticipate certified pharmacies that do not agree to public disclosure will communicate with the certified prescribers they wish to work with.

The REMS Assessment Plan is discussed in the following section.

**Reviewer's Comment:** *We agree with the Sponsors' proposal. The Supporting Document addresses all REMS requirements and provides sufficient clarification of implementation and maintenance of the REMS. The implementation requirements for pharmacies currently dispensing mifepristone under FDA's exercise of enforcement discretion during the COVID-19 PHE provide for continued use of these pharmacies without breaks in service. The communication strategy is also adequate given the efforts to reach both established certified prescribers and potentially new prescribers through professional organizations.*

*The Sponsors' plan to communicate which pharmacies are certified to certified prescribers is adequate. For the reasons listed in section 3.3.2.3, confidentiality is a concern for REMS stakeholders. Disclosure of pharmacy certification status should be a choice made by individual certified pharmacies. The Sponsors have indicated that there will be some certified pharmacies that have agreed to publicly disclose their status, making this information available to certified prescribers who wish to use a pharmacy to dispense mifepristone.*

#### 5. REMS Assessment Plan

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter.

The REMS Assessment Plan was revised to align with the modified REMS goal and objectives.

The goal of the Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

- a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
  - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.
- b. Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
  - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.
- c. Informing patients about the risk of serious complications associated with mifepristone.
  - This objective will be indirectly assessed using REMS Certification Statistics to avoid compromising patient and prescriber confidentiality. As part of the certification process, healthcare providers agree to:
    - Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained
    - Ensure that the *Patient Agreement Form* is signed by the healthcare provider and the patient
    - Ensure that the patient is provided with a copy of the *Patient Agreement Form* and the Medication Guide
    - Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record

The following revisions were made from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval letter:

The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.

REMS Certification Statistics metrics were added to capture certification numbers for program stakeholders to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. The total number of certified prescribers who certified with the wholesaler/distributor and the total number of certified prescribers who submitted a *Prescriber Agreement Form* to certified pharmacies were added to capture the additional method of prescriber certification. The number of newly certified prescribers and the number of active certified prescribers (i.e., those who ordered mifepristone or submitted a prescription during the reporting period) were added. Metrics were also added to capture the total number of certified, newly certified, and active certified pharmacies as well as the total number of authorized, newly authorized, and active authorized wholesaler/distributors.

Drug Utilization Data metrics were added to obtain information on shipment and dispensing of mifepristone. Metrics were added to capture the total number of tablets shipped by the wholesaler/distributor and the number of prescriptions dispensed.

REMS Compliance Data metrics were added to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. These metrics capture program deviations and evaluate overall if the REMS is operating as intended. Metrics include certified pharmacies and wholesaler/distributor audit results and a summary of instances of non-compliance and actions taken to address non-compliance. Prescriber compliance metrics were added to assess if prescribers are decertified along with reasons why. Pharmacy compliance metrics were added to assess if prescriptions were dispensed that were written by non-certified prescribers or if mifepristone tablets were dispensed by non-certified pharmacies as well as the number of pharmacies that were decertified along with reasons why. Wholesaler/distributor metrics were added to assess if shipments were sent to non-certified prescribers and non-certified pharmacies and corrective actions taken. The audit plan and non-compliance plans will be submitted for FDA review within 60 days after the REMS modification approval.

The Sponsors were asked to develop an assessment of prescription delivery timelines to determine what percentage of prescriptions were delivered on time (within four calendar days) and what percentage were delivered late (more than four calendar days) along with the length of the delay and reasons for the delay (e.g., mifepristone is out of stock shipment issues, other). The protocol for this assessment will be submitted for FDA review within 60 days after the REMS modification approval.

The revised REMS Assessment Plan is in the Appendix.

**Reviewer's Comment:** *We agree with the Sponsors' proposed REMS Assessment Plan.*

## 6. Discussion

The Sponsors submitted changes to the REMS to remove the requirement that mifepristone be dispensed only in certain healthcare settings (i.e., the "in-person dispensing requirement") and to add that certified pharmacies can dispense the drug in order to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. The REMS goal was updated to this effect. Changes were required for prescriber requirements and Sponsors to support the change in ETASU, and new pharmacy requirements were introduced.

The qualifications to become a certified prescriber have not changed as a result of the modification to the Mifepristone REMS Program; however, clarification has been provided for certain prescriber requirements and new prescriber requirements have been added to support pharmacy dispensing. Although certain responsibilities may be conducted by staff under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. In order to clarify this, revisions were made throughout the prescriber requirements and REMS materials to reflect that the certified prescriber is responsible for ensuring that the prescriber requirements are met. Additionally, the review team finds it acceptable that certified prescribers who wish to use a certified pharmacy to dispense mifepristone submit their *Prescriber Agreement Form* to the dispensing certified pharmacy (b) (4).

. The burden to prescriber and

pharmacy stakeholders of having certified prescribers submit the form directly to the certified pharmacy that will be dispensing the mifepristone is not unreasonable and has been minimized to the extent possible; it does not impact the safe use of the product. Prescriber requirements necessitated by the addition of some pharmacy requirements were added as well and include prescriber responsibilities in deciding whether or not mifepristone should be dispensed if the patient will receive the drug from the certified pharmacy more than four days after the pharmacy receives the prescription, and prescriber adverse event reporting requirements if a prescriber becomes aware of a patient death and the mifepristone was dispensed from a certified pharmacy. The addition of the latter requirements will ensure consistent adverse event data is relayed to the relevant Mifepristone Sponsor.

Changes were made to the *Patient Agreement Form*. Changes to the form were added to improve clarity of the safety messages. After further consideration, the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion has been removed from the *Patient Agreement Form*. The Medication Guide is not typically carried by patients and this information can be obtained at the point of care. Changes align with updates to labeling submitted with this modification.<sup>13, 14</sup>

The Agency and Sponsors agreed during this modification to focus on certification of pharmacies that can receive *Prescriber Agreement Forms* via email or fax to complete the prescriber certification process. The proposed pharmacy certification requirements also support timely dispensing of mifepristone. If the mifepristone is shipped to the patient, the REMS requires that it must be delivered within four calendar days from the receipt of the prescription by the pharmacy; if the patient will receive the mifepristone more than four calendar days from pharmacy receipt of prescription, the REMS requires the pharmacist to confirm with the certified prescriber that it is still appropriate to dispense the drug to the patient. This allows prescribers to make treatment decisions based on individual patient situations. A requirement to maintain confidentiality was also added to avoid unduly burdening patient access since patients and prescribers may not utilize pharmacy dispensing if they believe their personal information is at risk. Ultimately, the addition of pharmacy distribution with the proposed requirements will offer another option for dispensing mifepristone, alleviating burden associated with the REMS.

(b) (4)



The Agency reviewed the REMS in 2021, and per the review team's conclusions, a REMS modification was necessary to remove the in-person dispensing requirement and add a requirement that pharmacies that dispense the drug be specially certified; the review team concluded that these changes could occur without compromising patient safety. There have been no new safety concerns identified relevant to the REMS ETASUs that the applicants proposed modifying in their June 22, 2022 submissions since the REMS Modification Notification letters dated 12/16/2021. It is still the position of the review team that the proposed modification is acceptable.

Because the modification proposed include changes to the ETASU of the Mifepristone REMS Program, the assessment plan and timetable of assessments were changed. The assessment plan will capture information on pharmacy dispensing and provide valuable insight as to whether the program is operating as intended Annual assessments are consistent with other approved REMS modifications for major modifications necessitating extensive assessment plan changes.

As part of the REMS Assessment Plan, the REMS goal and objectives are assessed using Program Implementation and Operations Metrics, including REMS Certification Statistics and REMS Compliance Data. The metrics will provide information on the number of certified prescribers, certified pharmacies, and authorized wholesalers/distributors as well as if mifepristone is dispensed by non-certified prescribers or pharmacies. The Sponsors will use the indirect measure of healthcare provider certification to address the objective of informing patients of the risk of serious complications of mifepristone, due to concerns with prescriber and patient confidentiality. Although we typically assess whether patients are informed of the risks identified in a REMS through patient surveys and/or focus groups, we agree that the Sponsors' continued use of the indirect measure of healthcare provider certification adequately addresses the Mifepristone REMS Program objective of informing patients. In addition, because of these prescriber and patient confidentiality concerns, we believe it is unlikely that the Agency would be able to use the typical methods of assessment of patient knowledge and understanding of the risks and safe use of mifepristone.

## 7. Conclusions and Recommendations

The review team finds the proposed REMS modification for the Mifepristone REMS Program, as submitted on June 22, 2022, and amended on October 19, 2022 (Danco) and October 20, 2022 (GBP), November 30, 2022 (both), December 9 (both), and December 16 (both) acceptable. The REMS materials were amended to be consistent with the revised REMS document. The review team recommends approval of the Mifepristone REMS Program, received on June 22, 2022, and last amended on December 16, 2022, and appended to this review.

## 8. References

1. (b) (6) Clinical Review of SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909590.
2. (b) (6) Summary Review for Regulatory Action for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909594.
3. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909588.
4. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909587.
5. Approval Letter for SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909592.
6. (b) (6) REMS Review for mifepristone, NDA 020687. February 22, 2018. DARRTS Reference ID: 4224674.
7. Approval Letter for SE-20 REMS Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 4418041.
8. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the

Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

9. (b) (6) REMS Modification Rationale Review for mifepristone, NDA 020687. December 16, 2021. DARRTS Reference ID: 4905882.
10. General Advice Letter for the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, NDA 020687, April 15, 2022. DARRTS ID 4969358.
11. Format and Content of a REMS Document Guidance for Industry <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf>. Accessed on December 18, 2022.
12. Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception* 2022; 107:36-41. <https://doi.org/10.1016/j.contraception.2021.09.008>. This article was included in the literature review for the December 16, 2021 REMS Modification Rationale Review, while the article was still in press.

## 9. Appendices

REMS Document

Prescriber Agreement Form for Danco Laboratories, LLC

Prescriber Agreement Form for GenBioPro, Inc.

Patient Agreement Form

Pharmacy Agreement Form for Danco Laboratories, LLC

Pharmacy Agreement Form for GenBioPro, Inc.

Mifepristone REMS Assessment Plan

Initial Shared System REMS approval: 04/2019

Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg

Progestin Antagonist

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)  
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG**

**I. GOAL**

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

- a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
- b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
- c) Informing patients about the risk of serious complications associated with mifepristone.

**II. REMS ELEMENTS**

**A. Elements to Assure Safe Use**

1. Healthcare providers who prescribe mifepristone must be specially certified.
  - a. To become specially certified to prescribe mifepristone, healthcare providers must:
    - i. Review the Prescribing Information for mifepristone.
    - ii. Complete a *Prescriber Agreement Form*. By signing<sup>1</sup> a *Prescriber Agreement Form*, prescribers agree that:
      - 1) They have the following qualifications:
        - a) Ability to assess the duration of pregnancy accurately
        - b) Ability to diagnose ectopic pregnancies
        - c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
      - 2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
  - b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
    - i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
    - ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form*.

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<sup>1</sup> In this REMS, the terms “sign” and “signature” include electronic signatures.

- iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
  - iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
  - v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.
  - vi. If mifepristone will be dispensed by a certified pharmacy:
    - 1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.
    - 2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
    - 3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.
  - vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:
    - 1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.
    - 2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.
    - 3) Ensure that healthcare providers under their supervision follow guidelines i.-v.
  - c. Mifepristone Sponsors must:
    - i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.
    - ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:
      - 1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.
      - 2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.
    - iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.
    - iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.
    - v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.
- The following materials are part of the Mifepristone REMS Program:
- *Prescriber Agreement Form for Danco Laboratories, LLC*
  - *Prescriber Agreement Form for GenBioPro, Inc.*
  - *Patient Agreement Form*

2. Pharmacies that dispense mifepristone must be specially certified
  - a. To become specially certified to dispense mifepristone, pharmacies must:
    - i. Be able to receive *Prescriber Agreement Forms* by email and fax.
    - ii. Be able to ship mifepristone using a shipping service that provides tracking information.
    - iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.
  - iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:
    - 1) Review the Prescribing Information for mifepristone.
    - 2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:
      - a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.
      - b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.
      - c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
      - d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
      - e) Track and verify receipt of each shipment of mifepristone.
      - f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.
      - g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
      - h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
      - i) Maintain records of *Prescriber Agreement Forms*.
      - j) Maintain records of dispensing and shipping.
      - k) Maintain records of all processes and procedures including compliance with those processes and procedures.
      - l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.
      - m) Train all relevant staff on the Mifepristone REMS Program requirements.

- n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.
- b. Mifepristone Sponsors must:
  - i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.
  - ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.
  - i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
  - *Pharmacy Agreement Form for GenBioPro, Inc.*
3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.
- a. The patient must sign a *Patient Agreement Form* indicating that the patient has:
    - i. Received, read and been provided a copy of the *Patient Agreement Form*.
    - ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

## **B. Implementation System**

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:
- a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.
    - i. The distributors must put processes and procedures in place to:
      - 1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.
      - 2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.
      - 3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.
      - 4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.
      - 5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.
    - ii. Put processes and procedures in place to maintain a distribution system that is secure,

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

- iii. Train all relevant staff on the Mifepristone REMS Program requirements.
  - iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.
- b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.
2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.
  3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.
  4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.
  5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.
  6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.
  7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

### **C. Timetable for Submission of Assessments**

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

**MIFEPREX® (Mifepristone) Tablets, 200 mg**

**PRESCRIBER AGREEMENT FORM**

Mifeprex\* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To **become a certified prescriber**, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies:**
  - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

**Prescriber Agreement:** By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

***Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:***

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting [www.earlyoptionpill.com](http://www.earlyoptionpill.com).

**In addition to meeting these qualifications, you also agree to follow these guidelines for use:**

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.



\*MIFEPREX is a registered trademark of Danco Laboratories, LLC  
P.O. Box 4816-New York, NY 10185

1-877-4-EARLY-OPTION (1-877-432-7596) [www.earlyoptionpill.com](http://www.earlyoptionpill.com)

**DEAR273**

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Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: \_\_\_\_\_ Title: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Medical License # \_\_\_\_\_ State \_\_\_\_\_

NPI # \_\_\_\_\_

Practice Setting Address: \_\_\_\_\_

Return completed form to [Mifeprex@dancodistributor.com](mailto:Mifeprex@dancodistributor.com) or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]



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P.O. Box 4816-New York, NY 10185

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**DEAR274**

**2023 SUPP 001140**

PRESCRIBER AGREEMENT FORM

Mifepristone Tablets, 200 mg

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To **become a certified prescriber**, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies:**
  - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

**Prescriber Agreement:** By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

***Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:***

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free), or by visiting [www.MifeInfo.com](http://www.MifeInfo.com).

**In addition to meeting these qualifications, you also agree to follow these guidelines for use:**

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.



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**DEAR275**

**2023 SUPP 001141**

- If mifepristone will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: \_\_\_\_\_ Title: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Medical License # \_\_\_\_\_ State \_\_\_\_\_

NPI # \_\_\_\_\_

Practice Setting Address: \_\_\_\_\_

Return completed form to [RxAgreements@GenBioPro.com](mailto:RxAgreements@GenBioPro.com) or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]



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**DEAR276**

**2023 SUPP 001142**

## PATIENT AGREEMENT FORM

## Mifepristone Tablets, 200 mg

**Healthcare Providers:** *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

**Patient Agreement:**

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
  - a. I will take mifepristone on Day 1.
  - b. I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
  - heavy bleeding
  - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
  - a fever of 100.4°F or higher that lasts for more than four hours
  - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
  - severe stomach area (abdominal) pain or discomfort, or I am "feeling sick," including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol  
— these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

**Patient Signature:** \_\_\_\_\_ **Patient Name (print):** \_\_\_\_\_ **Date:** \_\_\_\_\_

**Provider Signature:** \_\_\_\_\_ **Provider Name (print):** \_\_\_\_\_ **Date:** \_\_\_\_\_

*Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.*

**01/2023**

**MIFEPREX®(Mifepristone) Tablets, 200mg**  
**PHARMACY AGREEMENT FORM**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

**By signing this form, as the Authorized Representative I certify that:**

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at [www.earlyoptionpill.com](http://www.earlyoptionpill.com); and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
  - Track and verify receipt of each shipment of Mifeprex.
  - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: \_\_\_\_\_ Title: \_\_\_\_\_



\*MIFEPREX is a registered trademark of Danco Laboratories, LLC

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**DEAR278**

**2023 SUPP 001144**

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Email: \_\_\_\_\_ Phone: \_\_\_\_\_ Preferred \_\_\_ email \_\_\_ phone

Pharmacy Name: \_\_\_\_\_

Pharmacy Address: \_\_\_\_\_

Return completed form to [Mifeprex@dancodistributor.com](mailto:Mifeprex@dancodistributor.com) or fax to 1-866-227-3343.



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**DEAR279**

**2023 SUPP 001145**

**PHARMACY AGREEMENT FORM****Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

**By signing this form, as the Authorized Representative I certify that:**

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at [www.MifeInfo.com](http://www.MifeInfo.com); and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
  - Track and verify receipt of each shipment of mifepristone.
  - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: \_\_\_\_\_ Title: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Email: \_\_\_\_\_ Phone: \_\_\_\_\_ Preferred \_\_ email \_\_ phone

Pharmacy Name: \_\_\_\_\_

Pharmacy Address: \_\_\_\_\_

Return completed form to [RxAgreements@GenBioPro.com](mailto:RxAgreements@GenBioPro.com) or fax to **1-877-239-8036**.



The REMS Assessment Plan must include but is not limited to the following items.

**Program Implementation and Operations**

1. REMS Certification Statistics

a. Prescribers

- i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
- ii. Number and percentage of newly certified prescribers
- iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

b. Pharmacies

- i. Number of certified pharmacies
- ii. Number and percentage of newly certified pharmacies
- iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)

c. Wholesalers/Distributors

- i. Number of authorized wholesalers/distributors
- ii. Number and percentage of newly authorized wholesalers/distributors
- iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data

- a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
- b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data

- a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
  - i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
  - ii. The number of audits expected, and the number of audits performed
  - iii. The number and type of deficiencies noted
  - iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
  - v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)

- vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)
- b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:
  - i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)
  - ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):
    - 1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
    - 2. The source of the non-compliance data (e.g., self-reported, audit, other)
    - 3. A root cause analysis of the non-compliance
    - 4. Actions to prevent future occurrences and outcomes of such actions
  - iii. Prescriber compliance
    - 1. Number and percentage of certified prescribers who became decertified as a result of non-compliance
      - Provide a summary of reasons for decertification (provide for the current reporting period)
    - 2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
  - iv. Pharmacy compliance
    - 1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
    - 2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
    - 3. Number and percentage of pharmacies that became decertified as a result of non-compliance
      - Provide a summary of reasons for decertification (provide for the current reporting period)
    - 4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
    - 5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)
  - v. Wholesaler/distributor compliance
    - 1. Number of healthcare providers who successfully ordered mifepristone who were not certified
    - 2. Number of non-certified pharmacies that successfully ordered mifepristone
    - 3. Number of shipments sent to non-certified prescriber receiving locations
    - 4. Number of shipments sent to non-certified pharmacy receiving locations

5. Summary and analysis of any program deviations and corrective actions taken  
(provide for the current reporting period)

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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**Risk Evaluation and Mitigation Strategy (REMS) Memorandum**  
**REMS Modification: Removal of a Requirement and Addition of a Requirement**  
**U.S. FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

(b)(6)/PPI

(b)(6)/PPI

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**NDA/ANDA #s:** NDA 20687, ANDA 91178  
**Products:** Mifeprex, mifepristone, 200 mg tablets  
**APPLICANTS:** Danco, GenBioPro  
**FROM:** (b)(6)/PPI  
(b)(6)/PPI  
**DATE:** December 16, 2021

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Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifeprex was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H) and subsequently was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007. The Mifeprex REMS with elements to assure safe use (ETASU) was approved on June 8, 2011 and a supplemental efficacy application and REMS modification was approved on March 29, 2016. The Mifepristone REMS Program (a single, shared system REMS that currently includes NDA 020687 and ANDA 91178) was approved on April 11, 2019.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone. The current Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use include requirements for prescriber certification (ETASU A), that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient, indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone.

The requirement under ETASU C that mifepristone be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals, is referred to as the “in-person dispensing requirement.”

On January 31, 2020 the Secretary of Health and Human Services (HHS) declared COVID-19 a public health emergency (PHE) as of January 27, 2020. During the COVID-19 pandemic, there have been periods when the in-person dispensing requirement has not been enforced. From July

13, 2020 until January 12, 2021, enforcement was barred by an injunction issued in the *ACOG v. FDA* litigation. More recently, on April 12, 2021, the Agency stated its intent to exercise enforcement discretion with respect to the in-person dispensing requirement during the COVID-19 PHE, which is still ongoing as of the date of this review. These circumstances have provided additional information regarding the in-person dispensing requirement as there have been periods when the in-person dispensing requirement was not enforced.

As part of the May 7, 2021, joint motion to stay the *Chelius v. Becerra* litigation, the Agency agreed to undertake a full review the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).<sup>1</sup>

After consultations between the (b)(6)/PPI (b)(6)/PPI and the (b)(6)/PPI (b)(6)/PPI analyzing several different sources of information, including published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius* litigation, we determined that the approved REMS for mifepristone could be modified without adversely impacting patient safety. Importantly, our review did not identify any differences in adverse events between periods when the in-person dispensing requirement was being enforced and periods when that requirement was not being enforced. The data suggested that the requirements for prescriber certification (ETASU A) and the Patient Agreement Form (ETASU D) should be maintained, while the in-person dispensing requirement (under ETASU C) could be removed, to reduce the burden imposed by the REMS. In determining that the in-person dispensing requirement could be removed, we concluded that a new requirement for pharmacy certification (ETASU B) is necessary to ensure the benefits of the product outweigh the risks.

(b)(6)/PPI and (b)(6)/PPI assessment and recommendations were presented to the (b)(6)/PPI (b)(6)/PPI on November 2, 2021. The (b)(6)/PPI unanimously agreed with our recommendations.

For more detailed information on the review and assessments of the information, refer to the REMS Modification Rationale Review, jointly completed by (b)(6)/PPI and (b)(6)/PPI on December 16, 2021.

In conclusion, provided all other conditions of the Mifepristone REMS Program are met and that the other elements of the REMS are maintained (ETASU A and D), the following are required:

1. Modification of the Mifepristone REMS Program to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals. This would allow, for example, dispensing of mifepristone by mail, via certified prescribers or pharmacies, in addition to in-person

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<sup>1</sup> Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C .

We find that this provision is no longer necessary to ensure that the benefits of the drug outweigh the risks and that removing it will help minimize the burden of complying with the REMS on the healthcare delivery system.

2. Modification of the Mifepristone REMS Program to add a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

Based on the (b)(6)/PPI and (b)(6)/PPI determination that a modified REMS with the components described above is necessary to reduce the burden imposed by the REMS and ensure the benefits of mifepristone outweigh the risks, FDA is requiring submission of the proposed REMS modification within 120 days of the date of the notification letter.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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(b)(6)/PPI

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**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research**

(b)(6)/PPI

**Integrated**

(b)(6)/PPI

**Memorandum**

**Date:**

December 22, 2022

**Reviewers:**

(b)(6)/PPI

(b)(6)/PPI

(b)(6)/PPI

(b)(6)/PPI

(b)(6)/PPI

(b)(6)/PPI

**Product Name:**

Mifepristone 200 mg

**Subject:**

All Adverse Events

**Application Type/Number:**

NDA 020687; ANDA 091178

**Applicants:**

Danco Laboratories, LLC; GenBioPro, Inc.

(b)(6)/PPI

**#:**

2022-2987

## 1 INTRODUCTION

This integrated (b)(6)/PPI memorandum provides a summary of United States (U.S.) postmarketing adverse events that reportedly occurred from October 1, 2021 - December 3, 2022, with mifepristone use for medical termination of pregnancy.

For the purposes of this memorandum, we reviewed both the FDA Adverse Event Reporting System (FAERS) database and the published medical literature to identify adverse events that reportedly occurred from October 1, 2021 - December 3, 2022.

## 2 METHODS AND MATERIALS

### 2.1 CASE DEFINITION

**Inclusion Criteria:** Cases were included if an adverse event reportedly occurred from October 1, 2021 - December 3, 2022, with mifepristone use for medical termination of pregnancy in the U.S.

**Exclusion Criteria:** Cases were excluded if they did not meet the inclusion criteria specified above OR for any of the following reasons:

- Mifepristone was used for a reason other than medical termination of pregnancy
- The case occurred outside of the U.S.
- The adverse event(s) did not occur during the specified time period of interest
- Insufficient information provided for case assessment
- No adverse event was reported

### 2.2 FAERS SEARCH STRATEGY

We searched the FAERS database with the strategy described in **Table 1**.

<b>Table 1. FAERS Search Strategy*</b>	
Date of search	December 4, 2022
Time period of search	October 1, 2021 - December 3, 2022 <sup>†</sup>
Search types	RxLogix PV Reports Quick Query, RxLogix PV Reports Case Form Report
Product terms	Active Ingredient: Mifepristone
MedDRA search terms (Version 25.1)	All adverse events
* See <b>Appendix A</b> for a description of the FAERS database.	
† Follow-up information obtained by (b)(6)/PPI after December 3, 2022, was included in this memorandum if the case was initially reported to FAERS between October 1, 2021 - December 3, 2022.	
<b>Abbreviations:</b> MedDRA=Medical Dictionary for Regulatory Activities	

## 2.3 LITERATURE SEARCH

We searched the medical literature with the strategy described in **Table 2**.

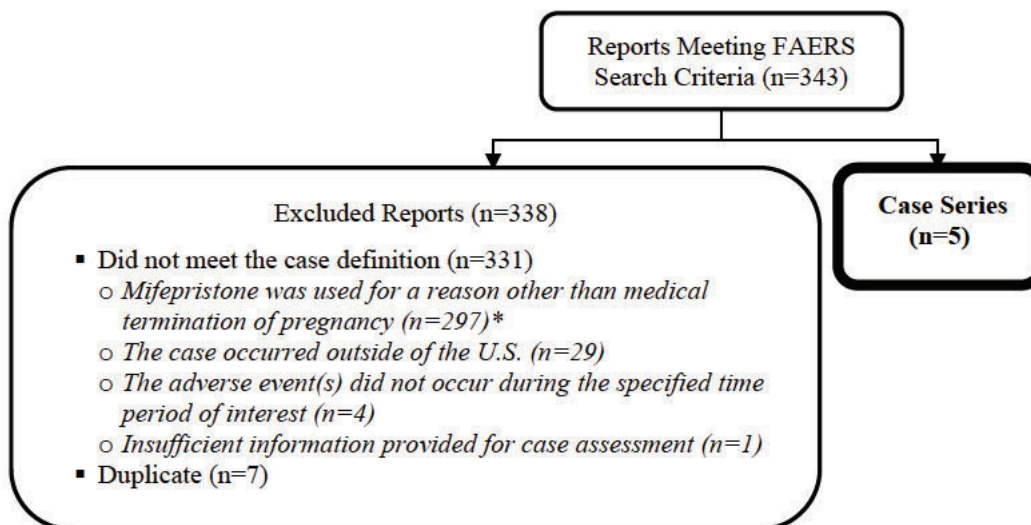
<b>Table 2. Literature Search Strategy</b>	
Date of search	December 4, 2022
Databases	Embase and PubMed
Search terms	Embase: ('mifepristone'/exp OR mifepristone) AND (2021:py OR 2022:py) AND 'case report'/de  PubMed: (("mifepristone"[MeSH Terms] OR "mifepristone"[All Fields] OR "mifepriston"[All Fields]) AND ("case reports"[Publication Type] OR "case report"[All Fields])) AND (2021:2022/12/3[pdat])
Years included in search	2021 and 2022

## 3 RESULTS

### 3.1 FAERS CASE SELECTION

The FAERS search retrieved 343 reports. After applying the case definition in **Section 2.1** and accounting for duplicate reports, five cases were identified in which an adverse event reportedly occurred from October 1, 2021 - December 3, 2022, with mifepristone use for medical termination of pregnancy in the U.S. (see **Figure 1**).

**Figure 1. FAERS Case Selection**



\* 295 reports documented the use of mifepristone for Cushing's syndrome (or related conditions) or specified the use of Korlym<sup>®</sup> and 2 reports documented the use of mifepristone for the management of early pregnancy loss.

We summarized the pertinent information from all five cases below. **Appendix B** contains a line listing of these five cases.

**FAERS Case # 21055005 (Duplicate Case # 21177969), Reported Adverse Event Date - May 18, 2022<sup>a</sup>**

A 26-year-old female at 7 weeks gestation per ultrasound ingested mifepristone 200 milligrams (mg) and was given misoprostol 800 micrograms (mcg) to administer, either via the buccal or vaginal route, 24 - 48 hours later for medical termination of pregnancy. It was specifically noted that the patient ingested the mifepristone at the clinic during her in-person appointment. The exact day/time of the misoprostol administration was unknown; however, it was known that it was administered vaginally. Approximately 12 days post-mifepristone ingestion (unknown number of days post-misoprostol), the patient committed suicide. The autopsy documented the cause of death to be the result of a “gunshot wound of head.” Of note, all psychiatric screenings completed during the patient’s clinic visit were reportedly negative for any psychiatric-related concerns. Additionally, the patient did not report any psychiatric history or history of depression.

**FAERS Case # 21073590 (Duplicate Case # 21252634), Reported Adverse Event Date - June 5, 2022<sup>b</sup>**

A 37-year-old female at 8 weeks 3 days gestation per ultrasound ingested mifepristone 200 mg followed by misoprostol 800 mcg buccally the next day for medical termination of pregnancy. It was specifically noted that the patient ingested the mifepristone at the clinic during her in-person appointment. No antibiotics or other medications were administered prior to her medical abortion. Approximately 8 days later, the patient presented to the hospital with complaints of significant abdominal pain and vaginal bleeding. She had not contacted the clinic about any of her symptoms prior to going to the hospital. Her white blood cell (WBC) count was found to be elevated at 29.3 K/uL (reference range: 4.0 - 11.0 K/uL) and the presence of copious, malodorous discharge was noted upon gynecologic examination; therefore, sepsis was suspected. Blood cultures were obtained, and intravenous (IV) antibiotics were initiated. The patient’s leukocytosis worsened despite being on antibiotics, and multiple interventions were documented over the course of her hospitalization, including additional antibiotics, hysterectomy, salpingectomy, and laparotomy. Her blood cultures were found to be positive for *Clostridium sordellii*. Ultimately, the patient expired 11 days post-mifepristone ingestion (10 days post-misoprostol). The death certificate documented the cause of death to be the result of sepsis/toxic shock syndrome secondary to *Clostridium sordellii*.

**FAERS Case # 21124769, Reported Adverse Event Date - July 8, 2022**

A 20-year-old female at 10 weeks gestation was believed to have ingested mifepristone 200 mg followed by misoprostol 800 mcg “under her tongue” (split into two 400 mcg doses) for medical termination of pregnancy. It was specifically noted that the patient “was given 1 pill by mouth at (b)(6)/PPI then instructed to go home and take 2 pills under her tongue, followed by 2 more pills under her tongue 4 hours later.” It was unknown if the patient had an ultrasound prior to mifepristone ingestion, the exact day/time of misoprostol administration was unknown, and the patient was unable to identify the medications she ingested as part of her medication abortion

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<sup>a</sup> This death case was not accounted for in the *Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2022* (which was completed by (b)(6)/PPI and finalized on November 9, 2022) as this case was not received by FDA until 7/7/2022.

<sup>b</sup> This death case was not accounted for in the *Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2022* (which was completed by (b)(6)/PPI and finalized on November 9, 2022) as this case was not received by FDA until 7/13/2022.

regimen; the reporting healthcare provider in (b)(6)/PPI suspected that the medications ingested were mifepristone and misoprostol based on information found on the (b)(6)/PPI clinic's website regarding their medication abortion protocol. Approximately 24 days later, the patient presented to the hospital (in (b)(6)/PPI), was found to have a high normal WBC at 15.23 (units were not specified; reference range: 4.5 - 15.3), elevated band neutrophils at 14 (units were not specified; reference range: 0 - 6), cervical tenderness, and a positive quantitative beta human chorionic gonadotropin level of 21.16 (units were not specified; reference range: < 4.83 non-pregnant). She was diagnosed as having a uterine infection and IV antibiotics were initiated. A dilation and curettage was also completed which "showed trophoblastic implantation site consistent with intrauterine conception and chronic endometritis." It is unknown if the patient had contacted the clinic prior to going to the hospital.

**FAERS Case # 21458187 (Duplicate Case # 21668113), Reported Adverse Event Date - September 7, 2022**

A 36-year-old female at 9 weeks gestation per ultrasound ingested mifepristone 200 mg followed by misoprostol 800 mcg vaginally later the same day for medical termination of pregnancy. It was specifically noted that the patient ingested the mifepristone at the clinic during her in-person appointment. No antibiotics or other medications were administered prior to her medical abortion. Telephone follow-up was completed approximately 7 days later, and no concerns were reported by the patient to the clinic. Approximately 26 days later (post-mifepristone ingestion), the patient presented to the hospital with complaints of abdominal pain and shortness of breath. She had not contacted the clinic about any of her symptoms prior to going to the hospital. She was found to be hypotensive and tachycardic; persistent vaginal bleeding and acute onset kidney injury were also noted. A potential pulmonary embolism was identified, and sepsis was suspected given the patient's clinical presentation and her initial elevated lactic acid of 6.1 mmol/L (reference range: 0.4 - 2.0 mmol/L). IV antibiotics were initiated; however, there was no documentation of blood culture results prior to initial antibiotic administration. The patient quickly decompensated despite multiple interventions, which included intensive care, intubation, and additional antibiotics. A bedside exploratory laparotomy was also deemed to be necessary and "necrosis of the uterus, liver, spleen, patchy necrosis of the small bowel and stomach, and complete necrotizing soft tissue infection of the retroperitoneum" was found. It could not be determined if the uterus was the source of the infection, but it was noted to be a possibility. Body fluid cultures ("abdominal purulence") initially identified gram-positive cocci in pairs and gram-negative rods but were then documented as "no growth after 5 days incubation." Blood cultures (post-antibiotic initiation) were negative. Ultimately, the patient expired 27 days post-mifepristone ingestion (27 days post-misoprostol). The preliminary cause of death was documented to be the result of "septic shock secondary to necrotizing fasciitis infection" ("septic shock with multi-organ failure with unknown definitive cause"). The patient's death certificate has been requested.

**FAERS Case # 21544690 (Duplicate Cases # 21643590, # 21682753, # 21706995), Reported Adverse Event Date - September 28, 2022**

A 24-year-old female at 8 weeks 5 days gestation per ultrasound ingested mifepristone 200 mg followed by misoprostol 800 mcg vaginally (exact day of misoprostol administration was unknown) for medical termination of pregnancy. It was specifically noted that the patient ingested the mifepristone at the clinic during her in-person appointment. No antibiotics or other

medications were administered prior to her medical abortion. Approximately 5 days later, the patient presented to the hospital with a 4-day history of nausea/vomiting, diarrhea, and abdominal pain. The patient reported a “normal amount” of vaginal bleeding. She had not contacted the clinic about any of her symptoms prior to going to the hospital. The patient was found to be dehydrated, and laboratory data showed hemoconcentration with acute renal failure; this was documented as being likely due to dehydration and IV fluids were administered. Sepsis was also suspected given her elevated lactic acid of 9.1 mmol/L (reference range: 0.4 - 2.0 mmol/L) and IV antibiotics were administered. Blood cultures were documented as being obtained per the healthcare provider’s notes; however, no blood culture order or results were found in the patient’s medical records. While awaiting transfer to a hospital with a higher level of care, the patient quickly decompensated despite multiple interventions, which included multiple fluid boluses, intubation, and cardiopulmonary resuscitation. Ultimately, the patient expired 6 days post-mifepristone ingestion (unknown number of days post-misoprostol). An autopsy was completed, and the cause of death was reported to be the result of “complications of septic abortion.” Postmortem blood cultures were reported to be negative for bacteria.

**Reviewers’ Comments:** *We identified a total of five FAERS cases in which an adverse event reportedly occurred from October 1, 2021 - December 3, 2022, with mifepristone use for medical termination of pregnancy in the U.S. Of note, all five cases reported that mifepristone was dispensed to and ingested by the patient while they were physically (i.e., in-person) at the clinic.*

*Of these five cases, one case reported suicide via a gunshot wound to the head, one case reported sepsis, and three cases reported both sepsis and death (i.e., death associated with sepsis). Of note, our review of the three cases reporting death associated with sepsis did not identify any new aspect of this known and labeled adverse event.*

*The risks of infection and sepsis are known and labeled adverse events with the use of mifepristone for medical termination of pregnancy. Language regarding the risk of infection and sepsis, in addition to specific clinical considerations (e.g., laboratory parameters that may be affected, signs and symptoms that may be present) and notation of the “sometimes fatal infections” or “very rare cases of fatal septic shock”, can be found in various sections of the prescribing information (e.g., BOXED WARNING, WARNINGS AND PRECAUTIONS) for the mifepristone products approved for medical termination of pregnancy.<sup>1, 2</sup>*

*The estimated number of women who have used mifepristone in the U.S. for medical termination of pregnancy since its approval on September 28, 2000, through the end of June 2022 is approximately 5.6 million women.<sup>3</sup> Since the U.S. approval of mifepristone for medical termination of pregnancy on September 28, 2000, there have been a total of eleven cases of death associated with sepsis (inclusive of two of the three cases summarized above reporting both sepsis and death) identified in the U.S. post-marketing setting (nine cases tested positive for *Clostridium sordellii*, one case tested positive for *Clostridium perfringens*, and one case had negative blood cultures).<sup>3</sup> Nine of the eleven fatal sepsis cases reported vaginal misoprostol use; two cases reported buccal misoprostol use. In the approved regimen for mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, misoprostol is administered by the buccal route and the prescribing information for the mifepristone products*

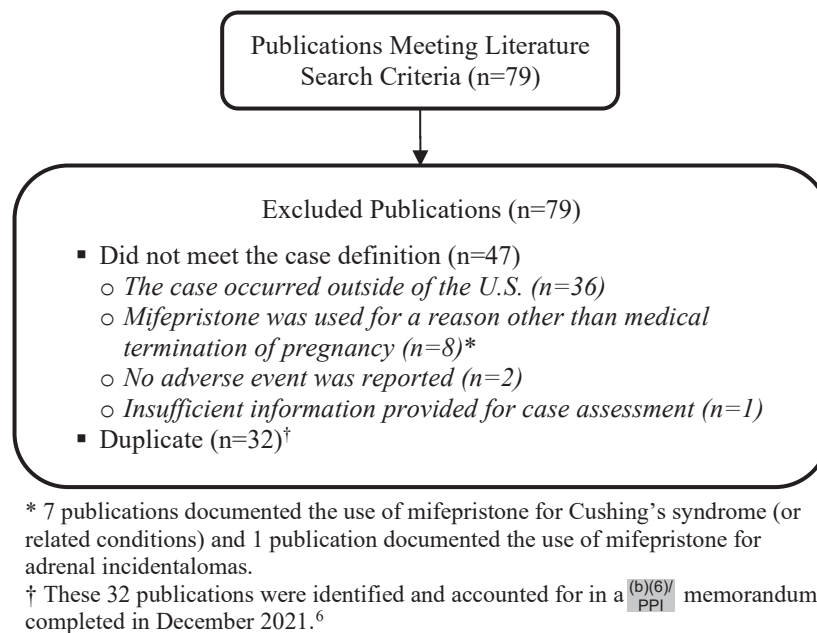
*approved for medical termination of pregnancy only reference the use of misoprostol via the buccal route; however, in clinical practice, vaginal administration is also used.*<sup>4, 5</sup>

*Of note, the aforementioned numerical analysis regarding the eleven cases of death associated with sepsis does not include the case in which the preliminary cause of death was reported to be the result of “septic shock secondary to necrotizing fasciitis infection” (“septic shock with multi-organ failure with unknown definitive cause”) as we have not yet received the requested death certificate. This death certificate is necessary to complete our analysis of this specific case given the uncertainty regarding the cause of infection.*

### 3.2 LITERATURE CASE SELECTION

The literature search retrieved 79 publications. After applying the case definition in **Section 2.1**, no relevant case reports of adverse events that reportedly occurred from October 1, 2021 - December 3, 2022, with mifepristone use for medical termination of pregnancy in the U.S. were identified in the published medical literature (see **Figure 2**).

**Figure 2. Literature Case Selection**



## 4 SUMMARY AND CONCLUSION

In summary, we identified five cases from FAERS in which an adverse event reportedly occurred from October 1, 2021 - December 3, 2022, with mifepristone use for medical termination of pregnancy in the U.S. Of these five cases, one case reported suicide, one case reported sepsis, and three cases reported both sepsis and death (i.e., death associated with sepsis). We did not identify any additional case reports in the published medical literature.

Based on the U.S. postmarketing data from FAERS reviewed in this memorandum, we have not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

## 5 REFERENCES

<sup>1</sup> Mifeprex (mifepristone) [package insert]. New York, NY: Danco Laboratories, LLC; April 2019. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/020687s0221b1.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s0221b1.pdf)

<sup>2</sup> Mifepristone [package insert]. Las Vegas, NV: GenBioPro, Inc.; February 2019. Available at: <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=b63fad9b-7f12-4400-9019-b0586054e534&type=pdf>

<sup>3</sup> (b)(6)/PPI Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2022. NDA 020687 and ANDA 091178. (b)(6)/PPI # 2022-2468. Finalized November 9, 2022.

<sup>4</sup> American College of Obstetricians and Gynecologists' Committee on Practice Bulletins - Gynecology, Society of Family Planning. Medication Abortion Up to 70 Days of Gestation: ACOG Practice Bulletin, Number 225. Obstet Gynecol. 2020 Oct;136(4):e31-e47. doi: 10.1097/AOG.0000000000004082

<sup>5</sup> National Abortion Federation - 2020 Clinical Policy Guidelines for Abortion Care. Available at: [https://prochoice.org/wp-content/uploads/2020\\_CPGs.pdf](https://prochoice.org/wp-content/uploads/2020_CPGs.pdf)

<sup>6</sup> (b)(6)/PPI Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b)(6)/PPI # 2007-525. Finalized December 16, 2021.

## **6 APPENDICES**

### **6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

#### **FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

**6.2 APPENDIX B. FAERS LINE LISTING OF ADVERSE EVENTS THAT REPORTEDLY OCCURRED FROM OCTOBER 1, 2021 - DECEMBER 3, 2022, WITH MIFEPRISTONE USE FOR MEDICAL TERMINATION OF PREGNANCY IN THE U.S.**

Case #	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s) *
1	7/7/2022	21055005	1	US-GenBioPro-2130636	Expedited (15-Day)	26	F	USA	DE
	8/4/2022	21177969	1	FDA-CDER-CTU-2022-62282	Direct	26	F	USA	DE
2	7/13/2022	21073590	1	US-GenBioPro-2130806	Expedited (15-Day)	37	F	USA	DE
	8/24/2022	21252634	1	FDA-CDER-CTU-2022-68089	Direct	37	F	USA	DE
3	7/23/2022	21124769	1	FDA-CDER-CTU-2022-58337	Direct	20	F	USA	HO, OT, RI†
4	10/13/2022	21458187	1	DL2022-02	Expedited (15-Day)	36	F	USA	HO, DE
	11/30/2022	21668113	1	FDA-CDER-CTU-2022-95327	Direct	36	F	USA	DE
	11/2/2022	21544690	1	US-GenBioPro-2134440	Expedited (15-Day)	24	F	USA	DE
5	11/25/2022	21643590	1	FDA-CDER-CTU-2022-93742	Direct	24	F	USA	DE
	12/5/2022‡	21682753	1	FDA-CDER-CTU-2022-96330	Direct	24	F	USA	DE
	12/9/2022‡	21706995	1	FDA-CDER-CTU-2022-98223	Direct	24	F	USA	DE

\*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.

† Although *Required Intervention* (RI) does not meet the regulatory serious definition per 21 CFR 314.80, this outcome is considered to be serious for the purposes of this memorandum.

‡ This FAERS case contains follow-up information obtained by <sup>(b)(6)</sup>/<sub>pp1</sub> for a case that was initially reported to FAERS between October 1, 2021 - December 3, 2022 (see **Table 1**).

**Abbreviations:** DE = Death, F = Female, HO = Hospitalization, OT = Other Medically Significant, RI = Required Intervention, USA = United States of America

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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